Mindfulness-based interventions for people with multiple sclerosis

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Abstract

Background:

Multiple sclerosis is a chronic neurodegenerative condition that can significantly impair length and quality of life. Comorbidity (the presence of additional chronic conditions) has been reported as common in multiple sclerosis and is associated with diagnostic delays, increased disability, and higher mortality rates in people with multiple sclerosis. Multiple sclerosis is a stressful condition, with a highly unpredictable disease course, often necessitating complex and unpleasant treatment regimens. Stress in multiple sclerosis raises the risk of significant mental illness, impacts negatively on quality of life, and may be associated with an increased risk of disease relapse (although the evidence supporting this latter link is limited). Current stress management strategies in multiple sclerosis are limited, with a recent systematic review identifying only one high quality study supporting the use of cognitive behavioural therapy. Mindfulness-based interventions have been demonstrated to help with stress management in other long-term conditions, such as anxiety and recurrent depression. Very little is known about the use and effectiveness of mindfulness-based interventions in people with multiple sclerosis.

Methods:

This thesis followed the United Kingdom Medical Research Council guidance (2008) on developing and evaluating complex interventions. The research commenced with an epidemiological study of comorbidity in multiple sclerosis using a nationally representative cross-sectional primary care database from Scotland (n=1,268,859, of whom 3,826 had multiple sclerosis). The analysis focused on 39 other long-term conditions, comparing prevalence rates for people with multiple sclerosis aged 25 or over versus matched controls, controlling for age, sex, and socio-economic status. Results are presented as odds ratios (ORs) with 95% confidence intervals (95%CI), and p values.

Secondly, a systematic review was conducted to evaluate the evidence for the effectiveness of mindfulness-based interventions in people with multiple sclerosis in terms of reducing perceived stress and other relevant secondary outcomes, including mental health, physical health, and quality of life. Study quality was determined using the Cochrane Collaboration quality assessment tool.

Following this, a phase-2 randomised controlled trial was undertaken, testing the feasibility of delivering a Mindfulness-Based Stress Reduction course to a group of (n=25) people with multiple sclerosis versus wait-list control (n=25). Primary patient report outcome measures were perceived stress (Perceived Stress Scale-10) and health-related quality of life (EQ-5D-5L). Secondary patient report outcomes included the Multiple Sclerosis Quality of Life Inventory, mindfulness (the Mindful Attention Awareness Scale), self-compassion (the Self-Compassion Scale-short form), and emotional lability (the Emotional Lability Questionnaire). Results are reported in 'p' values and effect sizes (ES - Cohen's 'd') with 95%CIs.

A linked qualitative process evaluation nested within the randomised controlled trial assessed Mindfulness-Based Stress Reduction instructor and participant experience through semi-structured interviews with 17 participants and the two instructors. In order to organise and summarise the data, the Framework Approach to thematic analysis was employed. The emergent themes from the thematic analysis were then scrutinised under the theoretical 'lens' of Normalisation Process Theory, as a means of conceptualising the data and assessing potential implementation issues.

Results:

Epidemiology People with multiple sclerosis in Scotland aged 25 years or over were more than twice as likely to have comorbidity of one or more long-term conditions than matched controls (OR 2.44; 95%CI 2.26-2.64). Mental health comorbidity was particularly prevalent in people with multiple sclerosis, being almost three times as common compared with controls (OR 2.94; 95% CI 2.75-3.14). Depression (OR 3.30; 95%CI 3.10 – 3.57) and anxiety (OR 3.18; 95%CI 2.89 – 3.50) were particularly common. As the number of physical health conditions rose in people with multiple sclerosis, so too did the prevalence of mental health comorbidity. Certain neurological conditions (epilepsy, pain, migraine, visual impairment) and gastrointestinal conditions (constipation, irritable bowel syndrome) were also more common in people with multiple sclerosis.

Systematic review Three published controlled outcome studies using mindfulness-based interventions in people with multiple sclerosis were identified. Only one study was of high methodological quality. The findings suggested that mindfulness-based interventions may improve quality of life, mental health (anxiety and depression), and some physical

outcome measures (fatigue, pain, standing balance), with effects lasting for up to six months post-treatment. Meta-analysis was not possible due to heterogeneity amongst studies. Since the systematic review was conducted, three further studies of mindfulness-based interventions in people with multiple sclerosis have been published. These studies were generally of low methodological quality, but they did add some further evidence that such interventions can improve scores for anxiety, depression, stress, pain, fatigue, co-ordination, balance, and quality of life. However, the overall weight of evidence supporting the use of mindfulness-based interventions in people with multiple sclerosis remains limited.

Randomised controlled trial The recruitment target of 50 participants was met within the pre-defined three-month window. Outcome measure completion rates were good immediately post-intervention (90%) and at study end-point, three months post-intervention (88%). However, participant attendance at the weekly 2.5 hours mindfulness sessions was only 60%, and average home practice times were less than the suggested amount of 45 minutes, six days per week.

In adjusted models (controlling for age, sex, deprivation, previous yoga/meditation experience) for primary patient-report outcomes immediately post-intervention, perceived stress scores improved with a large overall effect size (ES 0.93; $p<0.01$), and large effects were also evident on subscales of negative stress appraisal (ES 0.82; $p<0.05$), and on stress resilience items (ES 0.92; $p<0.05$). Quality of life scores showed only very small improvements overall (ES 0.17; $p=0.48$), with only the anxiety/depression subscale showing a small effect size immediately post-intervention (ES 0.41; $p=0.16$).

Secondary patient report outcomes showed improvements with large effect sizes immediately post-intervention in scores for depression (ES 1.35; $p<0.05$), positive affect (ES 0.87; $p=0.13$), anxiety (ES 0.85; $p=0.05$), and self-compassion (ES 0.80; $p<0.01$).

At study endpoint three-months post-intervention, adjusted models revealed that the beneficial effects on perceived stress and improvements in stress resilience had diminished to small effect sizes (ES 0.26; $p=0.39$, and ES 0.46; $p=0.05$ respectively). Quality of life scores showed negligible improvement overall (ES 0.08; $p=0.71$), but a small beneficial effect persisted on the anxiety/depression subscale (ES 0.26; $p=0.42$).

For secondary patient-report outcomes at study endpoint, the large effect sizes found immediately post-intervention for depression were no longer apparent (ES 0.01; p=1.00), but remained evident for positive affect (ES 0.90; p=0.54), anxiety (ES 0.82; p=0.15), and self-compassion (ES 0.83; p<0.05), with large effect size improvements also noted for mindfulness (ES 1.13; p<0.001) and prospective memory (ES 0.81; p<0.05).

Qualitative evaluation People who came on the Mindfulness-Based Stress Reduction course generally reported benefits, namely reduced stress, less pain, and improved relationships. Four main themes were identified in the thematic analysis: 1) 'Coming together for the course' 2) 'Doing the work' 3) 'Getting it, or not', and 4) 'Moving forward and improving the course'. Using the 'lens' of Normalisation Process Theory, these themes were further scrutinised, and potential barriers and facilitators to taking part were identified. Recommendations derived from this process included: a) inclusion of a pre-course orientation session in future courses to address participant expectations; b) making the course environment more disability-friendly; c) making the course materials more multiple sclerosis- and ability-appropriate; and d) embedding routine monitoring into future courses.

Conclusions:

The work of this thesis has demonstrated that among multiple sclerosis patients in Scotland, both physical and mental health comorbidities are common. There is limited published evidence supporting the use of mindfulness-based interventions in people with multiple sclerosis, but some indication that these interventions may improve anxiety, depression, stress, pain, fatigue, balance, co-ordination, and quality of life. Findings from the exploratory phase-2 randomised controlled trial suggest that delivering Mindfulness-Based Stress Reduction to people with multiple sclerosis under trial conditions is feasible with some evidence of likely effectiveness. Mindfulness-Based Stress Reduction generally appears to be acceptable, accessible, and implementable for people with multiple sclerosis, but an orientation session should be provided pre-course, and course materials may need to be carefully tailored to meet the complex needs of more disabled individuals with multiple sclerosis. These optimisation processes may lead to improved engagement and adherence with the mindfulness practices, which could potentially lead to more stable treatment

effects. Prior to proceeding to a phase-3 efficacy trial, such modifications should be piloted. More high quality research is required before definitive recommendations on the effectiveness of mindfulness-based interventions for people with multiple sclerosis can be made.

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Author's Declaration

I declare the contents of this thesis to all be my own work.

Listed below are the academic publications and presentations that have been made based upon the material in this thesis:

Journal publications

Simpson, R., Booth, J., Lawrence, M., Byrne, S., Mair, F. and Mercer, S., 2014. ***Mindfulness based interventions in multiple sclerosis-a systematic review***. *BMC neurology*, *14*(1), p.1.

Simpson, R.J., McLean, G., Guthrie, B., Mair, F. and Mercer, S.W., 2014. ***Physical and mental health comorbidity is common in people with multiple sclerosis: nationally representative cross-sectional population database analysis***. *BMC neurology*, *14*(1), p.128.

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Conference presentations

Oral-poster: '***Mindfulness-based interventions in multiple sclerosis: a systematic review***'. Mind and Life Institute European Symposium on Contemplative Studies. October 2013. Berlin, Germany.

Oral-poster: '***Stress management in multiple sclerosis: a PhD thesis'***. Neuroscience of Mindfulness conference. April 2014. University of Bangor, Wales.

Oral-poster: '***Mindfulness-Based Stress Reduction in people with multiple sclerosis – a randomised controlled trial****'*. NADEGs conference. January 2015. Stirling, Scotland.

Oral poster: '***Complex Interventions in Rehabilitation Medicine'***. European Congress on Neurorehabilitation. December 2015. Vienna, Austria.

Oral poster: '***Complex Interventions in Rehabilitation Medicine – Mindfulness-Based Interventions for People with Multiple Sclerosis***'. European Congress of Physical and Rehabilitation Medicine. April 2016. Lisbon, Portugal.

Definitions/ Abbreviations

AAN – American Academy of Neurology

ACC – Anterior Cingulate Cortex

ACT – Acceptance and Commitment Therapy

ADHD – Attention Deficit Hyperactivity Disorder

ADL – Activities of Daily Living

AL – Allostatic Load

ANCOVA – Analysis of Covariance

AUC – Area Under the Curve

BAI – Beck Anxiety Inventory

BBB – Blood-Brain Barrier

BCS – Bowel Control Scale

BDI – Beck Depression Inventory

BPD – Bipolar Disorder

BWCS – Bladder Control Scale

CBT – Cognitive Behavioural Therapy

CES-D – Center for Epidemiologic Studies - Depression

CI – Confidence Interval

CIS – Clinically Isolated Syndrome

CKD – Chronic Kidney Disease

COPD – Chronic Obstructive Pulmonary Disease

CONSORT – Consolidated Criteria of Reporting Trials

CNS – Central Nervous System

CNS-ELS – Center for Neurologic Studies Emotion Lability Scale

CRP – C-Reactive Protein

CSRI – Client Service Receipt Inventory

DASS-21 – Depression Anxiety and Stress Scale-21

DBT – Dialectical Behavioural Therapy

DMD – Disease Modifying Drug

EBM - Evidence-Based Medicine

EBV – Epstein-Barr Virus

EDSS – Expanded Disability Status Scale

ELQ – Emotional Lability Questionnaire

EQ-5D-5L - EuroQol

ES – Effect Size

FFMQ – Five-Facet Mindfulness Questionnaire

FSMC – Fatigue Scale of Motor and Cognitive functions

FSS – Fatigue Severity Scale

GAD-7 – Generalised Anxiety Disorder 7 scale

GC - Glucocorticoid

Gd+MRI – Gadolinium-enhanced Magnetic Resonance Imaging

GHQ – General Health Questionnaire

GP – General Practitioner

GPPC - General Practice and Primary Care

GPRD – General Practice Research Database

HADS – Hospital Anxiety and Depression Scale

HAQUAMS - Hamburg Quality of Life Questionnaire in Multiple Sclerosis (German)

HPAA – Hypothalamic-Pituitary-Adrenal Axis

HRQOL – Health Related Quality Of Life

HSCIC - Health and Social Care Information Centre

IBD – Inflammatory Bowel Disease

IBS – Irritable Bowel Syndrome

IC – Insular Cortex

IFNγ – Interferon-Gamma

IL-1β – Interleukin one Beta

IL-6 – Interleukin six

IL-17 – Interleukin 17

IL-23 – Interleukin 23

INS – Institute of Neurological Sciences (Glasgow)

ISD - NHS Information Services Division (Scotland)

ITT – Intention To Treat

IVIS – Impact of Visual Impairment Scale

LTC – Long-Term Condition

MAAS – Mindful-Attention Awareness Scale

MBI – Mindfulness-Based Intervention

MB-ART – Mindfulness-Based Art Therapy

MB-EAT – Mindfulness-Based Eating Awareness Therapy

MBCT – Mindfulness-Based Cognitive Therapy

MBRP – Mindfulness-Based Relapse Prevention

MBSR – Mindfulness-Based Stress Reduction

MDT – Multi-Disciplinary Team

MeSH – Medical Subject Heading

MFIS – Modified Fatigue Impact Scale

MHC – Major Histo-Compatibility

MHI – Mental Health Inventory

MND - Motor Neurone Disease

MPFC – Medial Pre-Frontal Cortex

MRC – Medical Research Council

MRI – Magnetic Resonance Imaging

MSIS-29 – Multiple Sclerosis Impact Scale-29

MSQLI – Multiple Sclerosis Quality of Life Inventory

MS – Multiple Sclerosis

MSS - Multiple Sclerosis Society

MSSS – Modified Social Support Survey

MBP - Myelin Basic Protein

NA – Not Applicable

NHS – National Health Service

NHS CIC – NHS Centre for Integrative Care

NHS GGC – NHS Greater Glasgow and Clyde

NICE – National Institute for health and Care Excellence

NNT – Number Needed to Treat

NPT – Normalisation Process Theory

NR – Not Recorded

PBA – Pseudo-Bulbar Affect

PDDS – Patient Determined Disease Steps

PDQ – Perceived Deficits Questionnaire

PES – Pain Effects Scale

PFC – Pre-Frontal Cortex

PNS – Parasympathetic Nervous System

POMS – Profile Of Mood States

PPMS – Primary Progressive Multiple Sclerosis

PPV – Positive Predictive Value

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSS – Perceived Stress Scale

PQOLC - Profile of health related Quality of Life in Chronic disorders (German)

PVD – Peripheral Vascular Disease

OR – Odds Ratio

QALY – Quality Adjusted Life Years

QLS – Quality of Life Satisfaction scale

QOF - Quality and Outcomes Framework

QOL – Quality Of Life

RCB - Robertson Centre for Biostatistics

RCT – Randomised Controlled Trial

REC – Research Ethics Committee

RRMS – Relapsing-Remitting Multiple Sclerosis

SAD – Social Anxiety Disorder

SCS-sf – Self-Compassion Scale-short form

SD – Standard Deviation

SES – Socio-Economic Status

SF-36 – Short-Form-36

SLE – Stressful Life Events

SMT-MS – Stress Management Therapy-Multiple Sclerosis

SNS – Sympathetic Nervous System

SPMS – Secondary Progressive Multiple Sclerosis

SPSS – Statistical Package for the Social Sciences

SRS - Stress Response Systems

SSS – Sexual Satisfaction Scale

STAI - Spielberger Trait Anxiety Inventory

TIA – Transient Ischaemic Attack

TICS-M - Telephone Interview for Cognitive Status-Modified

TM – Transcendental Meditation

TNFα – Tumour Necrosis Factor-Alpha

VAS – Visual Analogue Scale

VLPFC – Ventro-Lateral Pre-Frontal cortex

WHO - World Health Organisation

X^2 – Chi-squared test

Chapter 1 Introduction

1.1 Overview

The focus of this thesis is on the needs of people with multiple sclerosis (MS), and in particular whether mindfulness-based interventions (MBIs) may be beneficial. This thesis examines the epidemiology of comorbidity in people with MS in Scotland, the extent and scope of the evidence for effectiveness of MBIs, the feasibility and effects of conducting a trial of Mindfulness-Based Stress Reduction (MBSR) for people with MS, and explores participant views on MBSR. It highlights potential facilitators and barriers to wider implementation, and finally explores optimisation of MBSR prior to proceeding to a definitive phase-3 trial.

1.2 Background

MS is a chronic neurological condition characterised by neurodegenerative changes in the central nervous system (CNS) which result from damage to nervous tissue from pathological inflammation that targets the myelin sheaths surrounding nerves [1]. It is one of the most common neurological conditions to affect young adults and can lead to extreme levels of disability [1]. It is a condition that is on the increase, whilst disease mechanisms remain poorly understood and treatment options are limited, expensive, and potentially dangerous [1]. For reasons that are not totally clear, Scotland has the highest incidence and prevalence of MS worldwide [2]. The effects of the condition are manifold reflecting in part the variety of symptoms that nerve damage in distinct CNS locations can produce. They also reflect the diverse ways in which affected individuals react and adjust to having MS, including coping with the uncertainty that the condition brings [1]. MS can be a stressful condition, with negative consequences for the affected individual on a personal, social, and societal level. People with MS are thought to have particularly low health-related quality of life (QOL), more so than other, comparable long-term conditions (LTCs) [3, 4]. Stress is thought to play a key mediating role in the development of mood disorders and reduced QOL in people with MS [5], and may even affect adversely disease activity [6-8]. Mood disorders are thought to be very common [9], yet very little is known about how or why these evolve in people with MS, let alone how best they should be

treated [10]. Evidence for effective psychosocial interventions is limited, and a general consensus amongst researchers, clinicians, and patients is that novel and effective interventions are needed [10-12].

Mindfulness is a concept derived from ancient Oriental meditation techniques (Buddhist and Yogic) [13]. The construct has been variously adapted to operate as a stress reduction technique in Western medical settings for people with LTCs [14], although its contemporary usage now extends far beyond this scope [15]. MBSR is the format most widely used in a medical context, and is taught in a group format where participants are encouraged to explore their experiences through pre-defined meditation techniques, whilst adopting an open, non-elaborative and accepting attitude. Doing so is postulated to facilitate the development of 'mindful awareness' and this is thought to have a range of benefits in those with LTCs [13]. MBIs have been applied in a range of LTCs [16, 17], and have accrued a considerable evidence base for effectiveness, particularly in the treatment of recurrent depression [18]. Whether MBIs might help people with MS reduce stress and improve QOL has not been widely researched. Given the paucity of evidence for effective psychosocial interventions in this population, gaining a clearer understanding of whether and how MBIs might be of help can be seen as a relative research priority. This thesis has explored the area in detail. The section below highlights the specific aims and objectives addressed by this thesis.

1.3 Aims and objectives

The overall aim of this thesis was to characterise the needs of people with MS and the potential role, if any, for MBIs to reduce stress and improve QOL.

Specific research objectives were to:

1. Measure comorbidity in people with MS in Scotland by characterising the number and type of conditions compared with the general population.
2. Delineate the existing evidence for effectiveness of MBIs in people with MS by carrying out a systematic review.
3. Test the feasibility and effects of conducting a randomised controlled trial (RCT) of a MBI for people with MS, and clarify whether a future definitive trial is currently merited.

4. Explore the perceptions and views of people with MS participating in a MBI (MBSR)
5. Examine the potential barriers to and facilitators of implementing a MBI for people with MS

1.4 Thesis outline

This thesis set out to examine systematically the potential role of MBIs in people with MS. The plan was to study MBIs as a 'complex intervention', and thus methodology appropriate for this task was employed, based on the United Kingdom Medical Research Council (MRC) guidance [19] for developing and evaluating complex interventions. The MRC guidelines suggest that multiple and complementary research methods are likely to be required when researching complex interventions. This is in order to capture the broad range and scope of issues that can arise when trying to make sense of whether, how, and why a complex intervention may work in a study population. The MRC guidance [19] emphasises the importance of preparatory and developmental work before undertaking a definitive trial of effectiveness, where identifying issues at an early stage can pre-empt and avoid costly mistakes. Key features of the MRC framework involve having a clear distinction about the target population for the research question, a plausible working model for how the intervention may exert its effects, a thorough and up-to-date knowledge of the relevant literature for the intervention, and awareness of the potential for context to influence outcomes. This thesis followed the MRC guidance [19] in a systematic and iterative fashion, reflected in the chapter outlines below.

Chapter 2 provides the background chapter, and focuses first on the population under study i.e. people with MS. The chapter describes the aetiology, epidemiology, pathophysiology, and common signs and symptoms of MS. Particular emphasis is placed on the role played by stress. Existing treatments for stress management in MS are covered, noting the limitations that remain in the empirical literature on this subject. Next, attention turns to a potential treatment strategy i.e. mindfulness, or more specifically MBIs. The origins, purported mechanisms of action, evidence for effectiveness and use of MBIs in healthcare settings is then explored, with particular attention paid to their potential relevance for people with MS.

Chapter 3 outlines the methodology for the thesis, describing the overarching framework used [19]. The chapter also describes the specific research methods chosen for each subsection of the thesis.

Chapter 4 covers comorbidity in MS. The chapter describes in detail results from a secondary analysis of a nationally representative cross-sectional primary care database from Scotland.

Chapter 5 delineates the scope and extent of the existing evidence for effectiveness for MBIs in people with MS. The chapter describes the process involved in undertaking a systematic review, which included setting specific research questions, searching the literature in a rigorous and reproducible manner, collating results, and producing an accessible and informative report on findings. This chapter has both a quantitative and a narrative component, acting as an evidence synthesis, explaining why further work in this area is required.

Chapter 6 outlines the research process of undertaking a feasibility RCT of MBSR in a group of people with MS in Scotland. Key feasibility outcomes, such as recruitment, retention, adherence, outcome measure completion, follow-up, and likely effectiveness are covered in detail.

Chapter 7 focuses on qualitative feedback from the feasibility RCT. A thematic analysis on the feedback from participants is outlined in detail, where emergent themes are reported detailing how MBSR was experienced, and where it might be improved. This chapter also explored implementability using Normalisation Process Theory (NPT), to identify potential facilitators and barriers to the use of MBSR for people with MS in a NHS setting.

Chapter 8, the final chapter, is a general discussion of the research findings from the thesis as a whole. Discussion in this chapter focuses upon optimisation of MBSR, based upon the research findings from this thesis. Implications of the findings from this thesis for clinicians and researchers working in this area are considered, and future directions for research are suggested.

Chapter 2 Background

2.1 Introduction

This chapter introduces what is known about MS, in terms of its epidemiology, aetiology, pathology, and symptoms. LTCs can be stressful and this is particularly the case in MS. The mechanisms underlying stress in MS are discussed, noting the role that stress may play in diminishing QOL, increasing vulnerability to depression, and its possible impact on pathological disease processes. Following this, mindfulness is introduced as a potential treatment strategy for managing stress in people with MS.

2.2 Literature covered

The literature covered in this chapter reflects the focus of the thesis on the potential use of MBIs in people with MS. Primary searches in Pubmed which used the search terms 'stress*' AND 'multiple sclerosis', 'mindful*' AND 'multiple sclerosis', and 'comorbid*' AND 'multiple sclerosis' were carried out in August 2012. The results were accessed to gain a broad overview of what was known about stress in people with MS, about comorbidity in MS, and whether MBIs had been used as a treatment strategy. Additionally, weekly search update 'alerts' were set-up via Pubmed using these same search terms, whereby a weekly email was received detailing literature developments. References from key papers were used in a 'snowballing' manner, where interesting citations were retrieved and reviewed for relevance.

2.3 Multiple sclerosis – epidemiology, aetiology, and pathology

2.3.1 Epidemiology

MS is characteristically spilt into two main categories [20]:

1. Relapsing Remitting MS (RRMS), where periods of disease quiescence are interspersed between exacerbations. Relapses are unpredictable, vary widely

in duration and severity, and can leave people with significant residual disability. However, in others, recovery from a relapse may mean a return to a functional level approximate to their pre-exacerbation state.

2. Progressive MS, which is by convention spilt into cases progressive from the outset (Primary Progressive MS – PPMS), or those that become progressive against a background of RRMS (Secondary Progressive MS – SPMS).

Around 80% of cases fall into the RRMS category. A typical RRMS pattern of relapses is usually superseded by SPMS, a progressive stage that is most associated with the development of disability [20]. Roughly 20% of cases of MS are progressive from onset, where the disease evolves more rapidly (PPMS) [20]. Around 25% of people with MS do not develop much impairment in activities of daily living (ADL), but 60% of people are no longer able to walk after 20 years with the condition. About 15% progress very rapidly to severe disability [20, 21].

It is thought that there are around 2.5 million people with MS worldwide, and around 127,000 in the UK [20, 22]. Worldwide incidence is estimated at seven per 100,000 per year, with a prevalence of roughly 120 per 100,000, which varies geographically. For reasons that remain unclear, Scotland has the highest incidence per capita worldwide (12/100,000 per year) [2, 23], and similarly high prevalence (203-219/100,000) [23]. This creates a significant health care burden [24]. The global lifetime risk is estimated at 1 in 400, and peak age at diagnosis is 20-40 years, making it one of the most prevalent causes of neurological disability among young adults [1].

MS is commoner in females (around 2-3:1), although the exact sex ratio can fluctuate in diverse regions around the globe [24, 25]. As compared to men, women are two and a half times more likely to develop an RRMS course. In PPMS the incidence rate ratio approaches 1:1 [24, 26].

Research from Scotland suggests that MS tends to affect those of greater affluence [24, 27]. Systematic review evidence provides limited support for this finding, where in countries with high levels of socioeconomic inequality, such as the USA, Australia, and the UK, MS tends to affect more affluent people [28]. Speculative links have been drawn relating this to the so called ‘hygiene hypothesis’ (see section below).

2.3.2 Aetiology

A large number of factors are implicated in the aetiology of MS, but an exact underlying cause remains uncertain [25, 29-32]. Several environmental factors are suggested [33]. Latitudinal distance from the equator appears to be relevant, perhaps relating to effects on Vitamin D [24, 34]. There is also a seasonal predominance [35], particularly in Scotland, where higher rates appear in May and lower levels in November. This seasonal variation may relate to ultraviolet light exposure [1, 24]. Lifestyle factors such as smoking may contribute to disease development by triggering pro-inflammatory mechanisms, but this hypothesis remains unproven [36]. Dietary factors such as fish and coffee are suggested as protective for RRMS [37].

An underlying genetic susceptibility also seems highly likely in MS. Suspect factors include the gene coding for the endogenous inflammatory mediator Tumour Necrosis Factor-Alpha (TNF-α). The Major Histo-Compatibility (MHC) component on chromosome six, particularly genes encoding HLA-DRB*1501 and HLA-DRB5*0101, is also implicated [20, 24, 38]. However, MS is generally believed to be polygenic. Much attention has focused on identifying a unique trigger-antigen such as an infectious agent, possibly contributing to a series of disease outbreaks in genetically susceptible individuals. So far this search has been inconclusive [38].

Genetic precursors may combine with an environmental antigen trigger, for example Epstein-Barr Virus (EBV), which is present in over 99% of those with MS versus 94% in age-matched controls. Such infection might lead to pathological alterations in Blood-Brain-Barrier (BBB) integrity, and an organ/tissue-specific autoimmune reaction. The ‘hygiene hypothesis’ suggests that higher socio-economic status (SES) may denote less exposure to childhood infections, including EBV, with subsequent, more aberrant reactions to the infection [28]. Genetic and environmental factors could be cumulative, and possibly even synergistic within an individual case [38].

2.3.3 Inflammatory processes in MS

All types of MS are thought to have an inflammatory component in their pathology [32]. Theoretical pathological processes involve both the cell-mediated and humoral

components of the immune system, and may largely be determined by activated 'T' cell ingress into the CNS [38]. Such activated 'T' cells are potentially directed towards Myelin Basic Protein (MBP) in the myelin sheaths surrounding nerve cells. T cells appear to traverse the BBB via complex mechanisms, including BBB cell junction disruption, alterations in brain solute barrier function, with enhanced leukocyte adhesion and migration. These mechanisms are more likely if the BBB has been exposed to generic inflammatory cytokines such as Interferon-Gamma [IFN-γ], TNF-α, and/or Interleukin-1-Beta [IL-1β]. Once activated, T cells arrive in the CNS and stimulate microglia, the CNS macrophage. These then re-present the myelin protein to the T cells, thus completing a toxic autoimmune, pro-inflammatory cycle targeting the myelin-oligodendrocyte complex [38]. The resultant CNS inflammatory response promotes further inflammation with proliferation of macrophages, feeding further release of inflammatory mediators [25, 38, 39].

It is worth noting that demyelination is potentially reversible, and in some cases this will mean a move from relapse into remission, with potential recovery of function. However, when the myelin inflammatory process is unabated, leading to nerve axon transection, then permanent CNS damage ensues. CNS inflammation in MS may follow episodes of peripheral inflammation, with peripheral inflammatory mediators travelling into the CNS through a leaky, incompetent BBB. In MS relapses, the major cytokines suspected are IFN- γ, TNF-α, IL-1β, and Interleukin six (IL-6), both in terms of BBB breakdown and CNS inflammatory responses. These markers are notably elevated prior to the onset of and during disease activity, and decrease during periods of remission. Other factors that are implicated include Interleukins 17 and 23 (IL-17, IL-23) [25, 38, 39] (Figure 2.1).

The proposed inflammatory cascade in MS is non-linear and complex, with several components having multiple, sometimes paradoxical actions, which are context-dependent [40]. For example, besides being potentially destructive to myelin and nerve cells, inflammation may also play an important role in re-myelination [20, 38-40]. This can render targeted interventions i.e. pharmacological anti-inflammatory agents as both helpful and unhelpful, in that most are designed to either diminish inflammation, or hinder ingress of inflammatory mediators into the CNS [41].

Figure 2.1 Complex, non-linear inflammatory pathways in MS

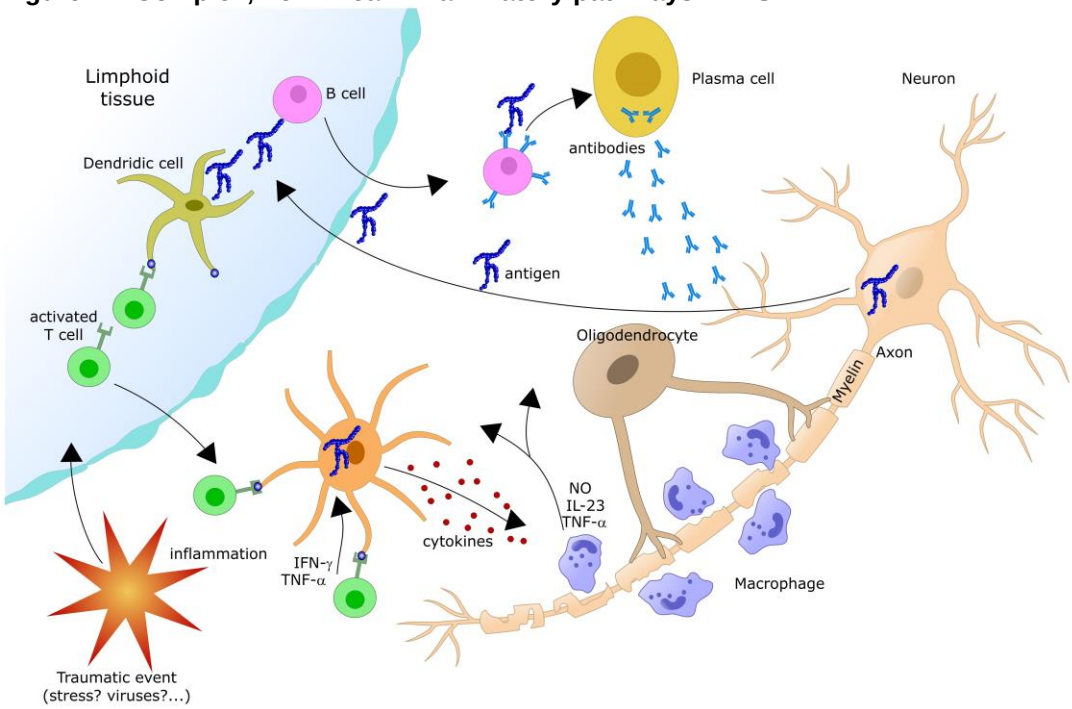


Figure 2.1: Reproduced with permission from Shutterstock images; complex non-linear inflammatory pathways linking stress, inflammation, and disease activity in MS

Breakdown of the BBB is a key step in the development of MS neuropathology, with a marked preponderance of neural inflammation noted at certain BBB locations [42]. Acute exacerbations in MS occur rapidly, within days, and correlate temporally with markers of acute inflammation. However, they can be short lived, with partial or complete recovery happening over weeks to months. Disease progression happens over years and probably represents either the cumulative result of repeated damage from numerous episodes of inflammation, or a continuous, lower-grade inflammatory process, with the end result being de-compensation in neural adaptive capacity [43].

In people with MS, permanent functional deficits are believed to relate to scarring, or ‘gliosed’ tissue, and diminished global functional reserve. However, during relapses, demyelinated axons do not conduct nerve action potentials as efficiently. This can result in cognitive impairment. The co-occurrence of other LTCs may compound this problem. For example, diabetes and cardiovascular diseases may also have cumulative detrimental effects on underlying CNS pathology.

2.4 MS signs and symptoms

2.4.1 Vulnerability, declining neurological reserve, and how this relates to the symptoms and signs in MS

There are a wide variety of symptoms and signs associated with MS including ataxia, bowel and bladder dysfunction, cognitive impairment, fatigue, mood disorders, pain, sensory disturbance, sexual dysfunction, spasticity and swallowing difficulties [20]. Even during periods of clinical quiescence, CNS tissues remain vulnerable in people with MS, where apparently innocuous stimuli can trigger problematic symptoms, such as pain or spasticity. Symptoms and signs are thought to result from a combination of localisable lesions, for example affecting the optic nerve, brainstem, cerebellum, or spinal cord, and the brain's adaptive capacity being impaired by overall lesion load. This may manifest in different ways, one example being fatigue [20]. Demyelination can cause spontaneous neural discharges, some of which create obvious signs and symptoms, and others that are more subtle [20]. Symptom interpretation at this level can be difficult for the individual, with each experience potentially heralding a relapse, or disease progression. Demyelinated axons are more vulnerable to environmental stimuli, such as changes in temperature, or simple touch. Such stimuli can create enhanced 'cross-talk' with neighbouring demyelinated axons, creating paroxysmal symptoms, such as pain, in-coordination, and spasticity [20].

2.5 Goals of treatment

2.5.1 Beyond pharmacology

Guidance from the UK National Institute for Health and Care Excellence (NICE) suggests that patient-centred care should be a priority for people with MS [44]. The guideline strongly emphasises the need for timely, co-ordinated, and evidence-based information and support. They promote well co-ordinated multidisciplinary care, with targeted symptom management and rehabilitation. The goal is for the individual to experience an integrated network of care [44]. Such integrated care, where all care sectors are working seamlessly for the individual, can be further enhanced with an aim for the individual patient also to experience 'integration', and the concept of '*no*

health without mental health' emphasises the importance of treating the underlying person, not just the disease in LTCs, such as MS [45]. Compston and Coles [20] suggest that the goal of treatment is to decrease the frequency and detrimental effects of relapses, to ameliorate symptoms, offset disability, and to promote tissue repair.

In the UK National Health Service (NHS), physical treatments for MS tend to be delivered by specialist Consultant-led multi-disciplinary teams (MDTs). In the early stages of disease this often involves the patient taking biologic disease modifying drugs (DMDs) that require close monitoring and have serious potential side effects, such as the re-activation of latent CNS infections that can (paradoxically) cause a neurodegenerative condition similar to MS [41]. Following periods of disease relapse or progression people with MS may require care in specialist rehabilitation centres over prolonged periods, and as disability becomes more advanced, then long term community care or care in a nursing home may be required. Specialist MS Nurses provide an enhanced service for patients and family members, and General Practitioners (GPs) may become involved at any stage [20, 46].

A recent high quality systematic review (n=29 studies) concluded that in order to reduce the economic burden associated with MS, treatments with the potential to limit the frequency and severity of relapses, and ultimately disease progression should be prioritised. However, all of the studies came from countries with readily available economic data (Europe, North America, and Australia) making wider applicability of findings limited [46]. Rising DMDs costs were cited as a major concern, the authors suggesting an urgent need for cost-effectiveness and comparative-effectiveness studies for new treatments.

2.6 Comorbidity in MS

Comorbidity has been defined as the presence of one or more medical conditions in an individual, in addition to a specified 'index' condition [47]. First documented some 40 years ago [48], it is a specialists' concept. For example, a Diabetologist will consider a patient with diabetes, depression, and arthritis as being a diabetic (index condition) with comorbidities (depression and arthritis). Mulitmorbidity, a related concept, is defined as the occurrence of two or more medical conditions within the

same individual, without there being a single condition ordered as the 'index' [47]. This term is better suited to generalist doctors, such as GPs who deliver continuous care centred on the patient as a person. Thus, a patient with diabetes, depression, and arthritis would be classified as multimorbid, without assuming that any of the conditions is more important to the patient than another.

Having multiple chronic conditions is believed to be stressful [49]. Recent epidemiological evidence from Denmark suggests that the co-existence of stress and multimorbidity is associated with excess mortality [50]. In a population-based cohort of 118,410 people, researchers found that after adjusting for SES, disease severities, and lifestyle factors, perceived stress impacted on mortality rates in a dose-dependent manner. High stress levels were associated with 69 excess deaths in those with one or less LTC, 128 in those with 2-3 LTCs, and 255 for those with four or more [50].

In this thesis, MS has been treated as the 'index', with other conditions being seen as comorbidities, including various other chronic conditions. The World Health Organisation (WHO) has defined chronic conditions as any: '*health problems that require on-going management over a period of years, or decades'* [49]. People with MS may have many other co-morbid medical and/or psychiatric conditions as part of their 'disease complex'. Mood disorders are common, anxiety and depression being particularly prevalent [51].

2.7 MS and stress – psychological and physical perspectives

2.7.1 Emotional turmoil, perceived stress, and quality of life

Emotional regulation depends upon awareness, understanding, and the ability to influence one's emotional state [52]. People with MS have difficulties in this area, where impaired emotional regulatory skills are implicated in diminished QOL [53]. There is evidence that emotional perception and processing of affective cues, such as social cognition, empathy, and theory-of-mind are abnormal from an early stage in the illness, even when age, sex, disease severity, underlying depression and cognitive dysfunction are controlled for [54, 55]. Such emotional difficulties can limit social

participation and correlate with impairment in psychological and social aspects of QOL [56]. There may be a neural basis for this in MS, such as damage or dysfunction in the insula and the ventrolateral prefrontal cortex (vlPFC), or impaired connectivity between the amygdala and the vlPFC and medial prefrontal cortex (mPFC) [5]. These altered neural dynamics may contribute directly to the enhanced vulnerability to depression in people with MS following stressful events [5].

Further evidence supporting an organic cause for emotional dysfunction in people with MS is that difficulties can range from perceptual problems, to difficulties with cognitive loading, to outright emotional lability and pseudobulbar affect (PBA). PBA is an extreme form of emotional dysfunction occurring in those with neurological injury and impairment such as stroke, traumatic brain injury, and MS. PBA refers to uncontrollable laughing or crying, out of context with the social scenario, incongruent with the person's inner emotional experience [57, 58].

However, it seems likely that emotional problems in people with MS are related to factors extending beyond damaged neural tissue, and in all likelihood have an important psychological and social basis too. Stress, mood and QOL are all intricately linked in people with MS. All have been shown to deteriorate from an early stage of the illness, in association with diminished ability for self-management [59]. Psychological stress has been shown to be an independent predictor of diminished QOL in people with MS [4] and perceived stress and depression both appear to play an important mediating role in diminishing QOL [60].

Dennison et al. [3] note that MS patients can be subject to an unpredictable disease course, distressing symptoms (i.e. sexual dysfunction and incontinence), challenging pharmacological treatments/side effects, physical and cognitive impairment, and social stigma. All of these can be stressful. Qualitative studies suggest the main psychological challenges relate to event unpredictability, a sense of loss, isolation, and emotional distress [61]. Making sense of symptoms can be difficult for people with MS and subjectivity features strongly [62, 63]. New symptoms can take on a unique significance, heralding potential relapse and/or progression, and the presence of depression increases medical symptom reporting and perceived illness severity [4].

People with MS experience more pronounced psychological distress than people without, emotional distress being reported as three times as common compared with healthy controls [64]. This has been reported as independent of disability level, although stressors and responses are thought to change as the disease progresses, with physical disability being a greater source of stress early in the illness, and cognitive dysfunction a more prominent stressor as disability accumulates [4].

In their operational model for stress appraisal and coping, Lazarus and Folkman [65] propose that individual cognitive appraisal is of central importance in determining each person's unique response to stress. They suggest that distressing emotions emerge as a consequence of situations that the individual perceives/appraises as being stressful. This view fits with other pre-eminent contemporary models which likewise emphasise the importance of individual perception/appraisal on downstream stress responses, be these psychological or biological [66, 67].

Folkman and Lazarus [68] suggest that coping can be seen as any patient behaviour(s) designed to alleviate, tolerate, or overcome the various demands, problems and burden that having chronic disease can bring forth. Individual psychological coping strategies can mediate the relationship between stress and coping in MS [69]. However, social/environmental context is also important for people with MS, where social support can protect against the deleterious impact of stress [69]. Loss of social function through MS appears to mediate between stress associated with the condition, and the development of depression [70]. Successful coping, or adaptation, depends upon how the individual appraises the situation and its salience, or meaning to them, but also how and to what extent the individual can access effective resources, such as social support or psychological interventions [68].

The uncertain prognosis associated with MS [71] can pose problems for adaptation and coping, where new symptoms may represent an impending relapse, or may not. Subsequent high levels of contact with medical services, seeking out a diagnosis and/or treatment can lead to a perceived loss of control, and is reported as stressful for people with MS, especially when the emotional impact of their symptoms is not openly acknowledged by the healthcare provider [62]. Symptom uncertainty can predispose to anxiety and rumination. It is a strong predictor of depression in MS [5].

The relationship between stress, emotions, and function in MS is complex. People with MS who are depressed, anxious, suffer from subjective or objective cognitive impairment, or have greater physical disability report lower QOL [72, 73]. Higher perceived stress is associated with a greater sense of impairment physically and socially, and worse adjustment amongst people with MS [70]. Higher levels of emotional distress also correspond with diminished functional capacity in ADLs [69]. Cognitive impairment is a common occurrence in people with MS [74], but separating out objective deficits from those that are more 'functional' is difficult, where depression and fatigue can complicate matters. Amongst these factors, depression and physical disability are reported as the strongest determinants of QOL [73, 75].

Folkman and Lazarus [68] posit that controllable stressors promote coping that is 'problem-focused', whilst those that are uncontrollable generate 'emotion-focused' strategies. Emotion-focused strategies in people with MS are linked to a greater risk of depression [5]. In contrast, problem-focussed coping is thought to enhance sense of control, and lessen sense of distress. Similarly, health locus-of-control is important in people with MS, where a higher sense of control over stressors confers better self-care and social functioning, better illness adjustment, and lowered relapse rate [76, 77].

2.7.2 Emotions, behaviour and adjustment

Systematic review evidence suggests that the commonest behavioural symptoms in people with MS are emotional lability (43%), emotional irritability (38%), psychological inflexibility (26%), aggression (23%), apathy (22%), and euphoria (12%) [78]. These symptoms are all more common in people with MS than in healthy controls, but are comparable with other LTCs [78]. It is unclear whether these symptoms are primarily reactive, how they relate to disability level, and to objective markers of disease activity [78]. However, they can impact negatively on QOL and how the individual deals with such symptoms seems important. For example, a recent cross-sectional study (n=157) showed that after adjusting for age, gender, SES, comorbidity, type and severity of MS, the tendency towards internalisation of anger significantly impaired QOL [79]; an effect stronger in women than men [79].

Irvine et al. [80] characterise psychosocial adjustment to MS as '*the ability to foster a positive outlook on life, continuing to grow and develop in spite of MS'*. Systematic narrative review evidence suggests that perceived stress, illness uncertainty, including ambiguity around diagnosis, symptoms, and treatments, and emotion-focused coping styles are associated with worse adjustment in people with MS [3]. A recent meta-analysis reported adjustment disorder (a group of symptoms including stress, sadness, and hopelessness following stressful life events - SLEs [81]) as the commonest behavioural impairment in people with MS [78].

Disease course in MS can affect psychological adjustment. For example, patients describe how a rapidly progressive course, or multiple relapses can be particularly stressful, and how adaptation and adjustment under such circumstances are challenging [62]. Certain psychological differences between patients serve as reliable predictors in this regard. Jopson and Moss-Morris [82] describe how a patient's unique illness representation, or how she characterises her condition, can have significant impact on mental health, fatigue, self-esteem, and social function. They suggest that seeing the illness as being physical in nature, as opposed to a result of psychological factors, is associated with better adjustment. Further, Dennison et al. [3] stress the importance of co-operation with health professionals in addressing health behaviour, those who engage being more likely to have better adjustment.

2.7.3 Psychological therapy in MS

Cognitive Behavioural Therapy (CBT) techniques have the most evidence for effectiveness for treating psychological symptoms in people with MS, particularly depression [10, 11, 83]. However, effective psychological treatments for anxiety are very limited [10]. As in other chronic medical conditions, effect sizes for CBT in MS are typically medium in magnitude [10]. Evidence supporting the use of pharmacological interventions in MS such as anti-depressants is sparse, with the incidence of side effects high [10, 84]. From an academic perspective, reviews consistently suggest that a wider range of evidence-based and patient-centred treatments is needed [10-12, 85]. From a patient perspective, people with MS value new information and techniques for coping [62]. From a clinical perspective, psychological therapy is seen as an important part of integrated care for people with

MS, especially where anxiety or depression exist [44]. Standard psychological input in the primary care setting is one potential treatment source, but is not always freely available, or accessible [86, 87], and in some cases specialist neuropsychological input is required [88]. Ideally, an intervention should be freely available, accessible, acceptable, tailored towards the needs of the individual, and highly effective [19].

2.7.4 Perceived stress and the immune system – conceptual overview, putative links, and potential relevance to people with MS

A further consideration in people with RRMS is the possibility that stress may increase vulnerability to MS relapse. A putative link between psychological distress and disease activity has been suggested since MS was described in the late 19th century [89]. However, until recently, there was very little evidence to substantiate this hypothesis. One problem is the heterogenous nature of stress definitions [8, 90]. From a healthcare perspective, a widely accepted contemporary definition of stress is:

> '*A state in which homeostasis is actually threatened or perceived to be so'* [67]

Put more simply, this definition suggests that the stress response systems (SRS) in the human body are in place to protect and sustain life. The process of homoeostasis maintains various vital bodily functions within a state of dynamic balance. Physical and environmental stressors can threaten this, an example being disruptions in blood pH, by triggering a host of compensatory physiological reactions. The same is also true for psychological stressors, even when the threat is illusory rather than 'real'. Stress responses are protective in the short term, but may be damaging left unchecked [91]. With this in mind, Irwin and Cole [92] define the primary physiological role of the CNS as being:

> *'..to perceive external physical and social conditions (the environment, broadly speaking), assess their implications for organismal well-being (fitness) and modulate the activity of internal physiological processes to optimally adapt to those external conditions'.*

They describe how this process of '*macro-environmental sensing*' influences the '*decision-making*' i.e. pro-inflammatory or anti-inflammatory transcriptional activity in immune cells, such as leukocytes. Practically, this means whether/how to respond to threat in a complex, at times hostile environment, via the production of hormones/neurotransmitters, etc [92]. Put more simply, this model suggests that mental events can affect physical processes in the immune system, or physical body. Similarly, the reverse is also true, whereby immune system constituents i.e. cytokines, can exert profound effects on mental phenomena [93] and this may be particularly relevant where disordered interplay between the CNS and the immune system might contribute to disease states, such as in MS [32, 40, 94, 95].

This model implies that how an individual appraises a stressor can mediate the physiological stress response. Importantly, stress can be a good thing under certain circumstances i.e. '*eustress*' [96]. A similar view also applies in the case of 'adaptive plasticity', where in one scenario stress mediators can induce damage, but in another can drive forward beneficial change [97]. An illustrative example is the training effects from physical exercise, where 'stress', or exercise, leads to beneficial adaptive changes in the cardiovascular system, or 'fitness'. Comparable adaptive processes are also known to take place in immune physiology [32]. The ability to adapt to stress like this can be linked with the concept of developing 'resilience', meaning that an organism can mount a 'stress response' to a given stressor, but remain able to return to a healthy state thereafter, without lasting damage [97].

Stress is known to exacerbate CNS inflammation in general, and is implicated in the development of various neuropsychiatric/neurodegenerative conditions [98]. The development of inflammation via stress may trigger a process of excitotoxicity, acutely disordering calcium homeostasis and precipitating cell death. Excitotoxicity is one of many potential mechanisms/pathways for the neural damage seen in MS [98].

Acute stress has reasonably predictable neurobiological consequences, including activation of the hypothalamic-pituitary-adrenal axis (HPAA), and the sympathetic nervous system (SNS). Both have important short-term roles in homeostasis and immune competence, with protective and adaptive effects [99]. Both also have more problematic long-term roles in the pathogenesis of mental health conditions, such as

anxiety and depression, where SLEs are major risk factors for developing these conditions [100, 101]. Acute stress enhances immune system activity, with greater responses in both the Th1, pro-inflammatory, and the Th2, more anti-inflammatory, subdivisions [102]. Both Th1 pro-inflammatory effects and Th2 Mast cell-mediated BBB breakdown responses are implicated in MS pathology [98].

On the other hand, chronic stress is believed to be immunosuppressive, with associated HPAA dysfunction and peripheral resistance to glucocorticoids (GC) [102]. HPAA dysfunction is a common factor in both chronic stress and depression [101]. Of particular relevance to MS, chronic stress also appears to impair new nerve cell production, the protection of existing nerve cells, and nerve cell repair, although these effects may be reversible via early intervention [103].

2.7.5 Stress, resilience, and health

Long term/incessant activation of the SRS has been associated with chronic ill health and 'allostatic load' (AL) [104]. AL is thought to contribute to various chronic conditions that are common in people with MS, including autonomic dysfunction, cognitive impairment, neurodegeneration, and depression [105]. Stress is widely regarded as a strong independent risk factor for depression [90, 101, 106], is implicated in the aetiology of other LTCs with inflammatory components i.e. cardiovascular diseases [107] and the metabolic syndrome [108] and is associated with increased mortality [50]. In those with LTCs, stress is frequently reported [109], and identifying stress resilience factors has been suggested as a research priority.

Resilience as a construct is not well defined, and both psychological [109], and biological components [110, 111] have been proposed. In psychological terms, resilience has been defined as '*the capacity of an individual to maintain/regain their mental health in the face of adversity/chronic illness*' [109]. A recent systematic review demonstrated the importance of accepting one's illness, adopting a determined attitude, having an internal locus of control, hardiness, hope, mastery, and self-efficacy, amongst psychological factors. Coping strategies that employed positive cognitive appraisal, spirituality, and active coping were beneficial, but having social support was the most important factor of all [109]. From a biological perspective,

resilience has been defined variously, in complex systems terminology [111] as how effectively a system returns to a healthy baseline, as depending on adaptive neural plasticity and allostatic regulatory systems [97], and also from the perspective of biological vulnerability, where certain genetic profiles may render an individual more or less resilient to SLEs [110]. It seems likely that both psychological and biological dimensions play a role in stress resilience. Stress resilience factors have not been systematically studied in MS, but two cross-sectional studies found that optimism and hardiness were predictive of coping and improved function [112, 113], whilst two qualitative studies suggested that a sense of spiritual purpose determines better adaptation to MS [114], as does benefit finding [115].

2.7.6 Can stress cause MS or make it worse?

Stress has been putatively linked to increased rates of MS relapse, the return of old symptoms, and with disease onset/causation [8]. In 2004 Mohr et al. [6] carried out a meta-analysis of longitudinal and case-control studies to quantify the proposed link between global SLEs and disease exacerbation in MS. They reported a consistent association, with findings based upon 14 empirical studies. Study quality was noted only as 'variable'. The weighted average effect size (ES) linking stress to relapses was modest (d=0.53), comparing favourably with treatment ESs for Interferon-β (d=0.30-0.36), an established pharmacological intervention for MS relapse [6].

In 2011, Artemiadis et al. [8] systematically reviewed longitudinal observational and case-control studies to assess the quality of evidence for the relationship between SLEs with MS causation, and with MS relapse. The Cochrane Newcastle-Ottawa scale assessed quality. Seventeen studies were included, eight of which featured in the earlier meta-analysis by Mohr et al [6]. Artemiadis et al. [8] did not conduct a meta-analysis due to heterogeneity in outcome measures of stress. The search criteria were limited (1980-2010), using only MEDLINE, and the search terms '*stress and multiple sclerosis*'. Study participant demographics and clinical characteristics were largely deemed as representative of the average MS population, with the majority being Caucasian females in their 30's, but there was a tendency towards shorter disease durations (<10 years) and low levels of disability. Other potentially important confounders such as SES, disease stage/severity were only controlled for in four of

the studies. Most studies utilised an environmental approach to stress i.e. self-report diaries, as opposed to biological measures, such as brain imaging, or psychological constructs e.g. perceived stress. Selection bias was an issue in case-control studies, as was a risk of recall bias when reporting on SLEs. No studies directly assessed perceived stress, and the use of objective biological outcome measures was minimal.

Findings from Artemiadis et al. [8] more strongly supported stress as a factor in relapse, where there were nine cohort and three case-controlled studies (n= 775), and 10/12 reported a positive association between SLEs and relapse. Relaxation and distraction were identified as moderating the impact of stress, and greater reactivity to perceived stressors was associated with increased chance of relapse, even when disease duration and symptoms were controlled for. Overall, it was reported that stress factors contributed about 10% to the variance in relapse rate. The evidence for stress causing MS was less, with one cohort and five case-controlled studies (n= 245). In both instances common stressors were family and social conflict, and for stress being related to disease onset, the strongest association was for sudden loss of a child, based on a large retrospective Danish cohort (n with MS = 21,062 versus 293,745 controls), where the hazard ratio was reported as 2.25 (95% CI: 1.32–3.81) [8].

In 1999 the American Academy of Neurology (AAN) proposed that in order to test convincingly the complex, inconsistent, and poorly understood relationship between stress and disease activity in MS, future prospective research should include an objective biological outcome measure such as serial Gadolinium-enhanced Magnetic Resonance Imaging (Gd+MRI). Gd+MRI is a highly sensitive measure of BBB breakdown/ on-going disease activity in MS, correlating with clinical relapse [116]. In 2012, Mohr et al. carried out a RCT using Gd+MRI to assess the impact of targeted stress management on disease activity [7]. Using a CBT-based Stress Management Therapy for MS (SMT-MS), they recruited individuals with RRMS (n=121) who were already established on pharmacological MS treatments, including individuals with a median Expanded Disability Status Scale (EDSS) score of 3.50 [range 0-6] [117]. Findings were of a 76.8% reduction in the development of new Gd+MRI lesions in the intervention group (n=60), with an odds ratio (OR) of 2.77 (95% CI 1.17-6.55; p=0.02), with an absolute risk reduction of 22.2%, and a number needed to treat of five. These findings were correlated to significantly reduced stress levels in

the intervention group, as measured via the Brief Inventory of Perceived Stress, but clinical neurology outcomes were not significantly improved.

In a secondary analysis of the Mohr et al. [7] study, Burns et al. [118] sought to clarify whether the value applied to stressors, i.e. negative/positive, major/moderate etc, impacted on clinical outcomes. Findings suggested that SLEs deemed by patients as 'positive' were associated with fewer new Gd+MRI lesions (OR 0.53; 95%CI 0.30-0.91), and a diminished likelihood of new/increase in size of T2 lesions (which represent overall lesion load) in the following 29-62 days (OR 0.74; 95% CI 0.55-0.99). In an earlier study, Mohr et al. [119] had found that 'moderate' stressful events, such as interpersonal conflict, disrupted routine, or reduced resources, predicted increased Gd+MRI enhancement. In the Burns et al. [118] secondary analysis, those events deemed as both 'major', such as physical threat/threat to family, and 'negative' were predictive for increased Gd+MRI lesions (OR 1.77; 95% CI 1.18-2.64), and new/increased size T2 lesions (1.57; 95% CI 1.11-2.23). However, 'moderate' SLEs did not correlate with disease activity and temporal measures ruled out brain lesions being related to subsequent positive, or major negative SLEs [118].

At this stage, it is impossible to say whether psychological stress can precipitate MS disease activity, or not. However, it seems likely that psychological stress has a deleterious effect on relapse frequency in RRMS, possibly through the effects of stress on underlying inflammatory mechanisms, and that individual interpretation of SLEs might mediate outcomes.

2.7.7 Patient report outcome studies of stress management interventions in MS

A 2014 systematic review on the efficacy of stress management interventions in people with MS reported that the majority of existing studies (n=5/8) had used a CBT approach, alongside some form of relaxation training [120]. One study used meditation, and the remaining two taught only relaxation. Five of the eight studies measured perceived stress, but QOL was measured in only three. Overall, methodology was reported as poor, and quality varied widely [120].

Using the AAN criteria, Reynard et al. [120] reported that the best evidence, i.e. 'Class 1', was for the SMT-MS used in the Mohr et al. [7] RCT described above. The grading was based upon rigorous trial methodology, and the fact that the outcome measurement was biological. Five studies were allocated AAN 'Class 3' evidence, less rigorous trial methodology and small sample sizes downgrading their quality.

Smaller than the Mohr et al. [7] study, Artemiadis et al. [121] randomised participants (n=61) to receive either relaxation training CDs, or usual care over eight weeks. Those receiving the intervention reported significantly improved QOL ($p<0.05$) and depression scores ($p<0.05$), and a positive trend for anxiety ($p=0.07$). This approach was mirrored in another RCT (n=66) using relaxation training CDs versus usual care, with the intervention arm reporting significant improvements in QOL ($p<0.05$) [122].

Another RCT (n=78) using mainly psycho-educational material and relaxation training on stress management found significant improvements in female MS patients on scores of mental health QOL ($p<0.01$) and perceived stress ($p<0.05$), but this was a heterogenous sample, not limited to MS [123]. The remaining two studies with ANA 'Class 3' evidence used CBT, were non-randomised, using interventions that were 13 [124], and six-weeks [125] in duration, respectively. They showed significantly improved anxiety ($p<0.01$) and depression ($p<0.05$) scores. The latter study sample in [125] was not confined to MS patients, limiting somewhat the relevance of results.

The final two studies with ANA 'Class 4' evidence used very small, non-randomised, non-controlled samples. Welch [126] (n=7) used a five week CBT intervention. Participants reported significantly less stress ($p<0.05$). Pritchard et al. [127] (n=12), used a Yoga-nidra technique weekly over six-weeks, reporting significantly lowered perceived stress ($p<0.001$). However, the latter sample was heterogenous, including 10 people with cancer, thus limiting its applicability.

To summarise, there is some limited evidence that stress management interventions may be effective at improving patient-report outcomes for stress, stress-related mental health comorbidities, and QOL in people with MS. However, most studies have been hampered by small sample sizes (range 7-121), questionable research methods, and poor characterisation of participant demographic and phenotypic spread. The

interventions, although mostly CBT-based, have varied widely. None of the studies examined mindfulness as a potential stress management intervention and it seems clear that more research for potential treatment strategies in this area is merited [120].

2.8 Mindfulness – a means of managing stress in MS?

Mindfulness is a Buddhist-derived insight meditation practice. The word is a translation of two Pali words 'Sati', meaning awareness, and 'Samprajanya', meaning clear-comprehension [128]. It has been defined in contemporary terms as applying an open, non-judgemental and non-elaborative quality of attention to awareness of the present moment [13]. A consensus definition in a health-care context remains elusive.

In psychological terms, Bishop et al. [129] define mindfulness as involving regulation of attention to the present moment, and adopting an attitude of acceptance, curiosity and openness to whatever experiences may come. Shapiro et al. [130], on the other hand, suggest that there are three qualities that must be cultivated when fostering mindful-awareness, including Intention, Attention, and Attitude. Alternatively, Baer et al. [131] describe a five-facet construct of trait mindfulness, perhaps reflecting distinct neural components. These include 1) non-reactivity towards inner experience, 2) observation of emotions, feelings and thoughts, 3) acting with awareness, 4) verbal description of experiences, and 5) non-judging of one's inner experience.

Drawing upon the models above, along with practitioner self-report and neuroimaging data, Holzel et al. [132] have proposed a working model for underlying neural mechanisms associated with mindfulness meditation, broken down into four components: 1) augmented attention regulation, 2) improved body awareness, 3) enhanced emotion regulation, and 4) change in perspective of the self (Table 2.1).

In the Holzel et al. [132] model, attentional skills are honed through first fostering mindful awareness in the meditation exercises, paying close attention to the content and variation in one's experiences, with a non-judgemental attitude. Body awareness is enhanced by 'tuning-in' to visceral sensations and emotions, for example, during mindful breath-awareness, mindful-movement, or 'the body-scan', which systematically trains the practitioner to shift attention from one body area to another.

Emotional regulatory skills are enhanced via adopting a non-directive, non-evaluative, and accepting approach to one's experiences, whereby exposure takes place, and avoidance is discontinued. Through experiencing one's self in this new way, implicit assumptions are brought to conscious awareness, which, it is asserted, can lead to a new perspective on the self, in terms of what does, and what does not constitute 'self'.

Table 2.1 Proposed neural mechanisms for mindfulness meditation (adapted from Holzel et al. [132])

Function	Mechanisms	Brain regions implicated
1. Attention regulation	The practitioner sustains their attention on a specified object of awareness, with any distractions being met simply with a return to the original focus of attention	Anterior cingulate cortex (ACC)
2. Bodily awareness	The meditation practices encourage an enhanced viscero-somatic awareness through focusing attention on internal bodily processes, such as the breath, or on emotion	Insular cortex (IC) Tempero-parietal junction (TPJ)
3. Emotion regulation	a) The practitioner attends to and adopts a non-judgemental attitude and acceptance towards their emotional experiences	Dorsolateral prefrontal cortex (dlPFC)
	b) The practitioner exposes themself to whatever experience is present, avoiding suppressing or elaborating on cognitive and affective responses	Ventromedial prefrontal cortex (vmPFC), Hippocampus, Amygdala
4. Change in perspective of the self	The practitioner detaches from their inherent and assumed identity with a fixed sense of self, thus diminishing its authority/validity	Medial prefrontal cortex (mPFC), Posterior cingulate cortex (PCC), insula, TPJ

Other authors broadly agree with the Holzel et al. [132] model and emphasise the key roles played in enhanced attention monitoring and emotion regulation by the prefrontal cortex (PFC), anterior cingulate cortex (ACC), and the insular cortex (IC) [128, 133, 134] (Figure 2.2).

Manuello et al. [135] suggest these brain areas represent the '*mindfulness-meditation network*', reflecting a move towards the study of distributed neural networks, beyond simply focusing on distinct brain locations. Tang et al. [134] concur with Holzel et al. [132] that mindfulness practices facilitate improved attentional control, better emotional regulation, and increased self-awareness, which together interact leading to a state of enhanced self-regulation. In the early stages, this is through the application

effortful practice, then later, by redirection of effort to reducing mind-wandering, and finally, in the more advanced stage, by being mindful with minimal effort.

Figure 2.2 Key brain areas involved in mindfulness meditation

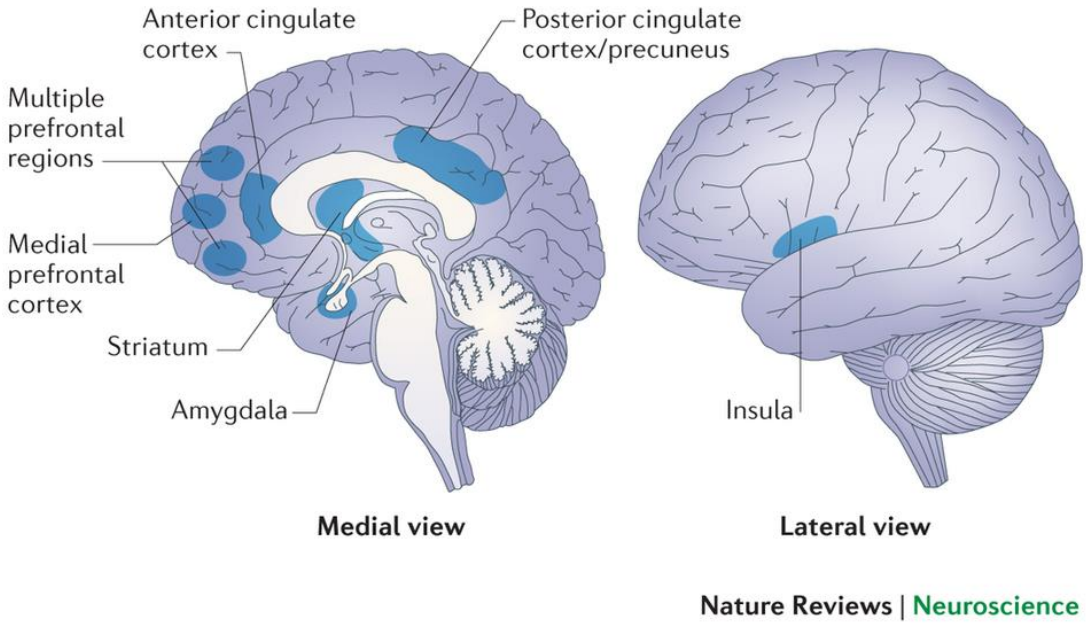


Figure 2.2: Brain areas postulated to be of importance in mindfulness meditation. These cover attentional control (ACC and the striatum), self-awareness (mPFC, posterior cingulate cortex, precuneus, and the IC), and emotion regulation (prefrontal regions, striatum, and limbic regions). *Reproduced with permission from: Tang, Yi-Yuan, Britta K. Hölzel, and Michael I. Posner. "The neuroscience of mindfulness meditation." *Nature Reviews Neuroscience* 16.4 (2015): 213-225.

Despite a rapid growth in the evidence base, neither the psychological nor neural mechanisms underlying mindfulness are entirely clear. In meta-analytic studies [136], the most effective emotion regulation strategies are 'top-down' cognitively-based i.e. problem solving and positive re-appraisal. These may apply in mindfulness-based cognitive therapy (MBCT) [137], but are less prominent in MBSR [13]. However, mechanistic models for mindfulness suggest that emotional regulation strategies may also stem from 'bottom-up' aspects of the training i.e. interoceptive practices, such as the body-scan, and somatoceptive practices such as mindful-movement, which recruit brain areas intricately linked to the PFC, the ACC, the IC, and the limbic system.

Whether mindfulness is distinct from more traditional cognitive concepts such as acceptance, emotional regulation, and/or selective attention is not known, but the models proposed by Holzel et al. [132], Tang et al. [134], and others [128, 133, 135] at least suggest some functional overlap [138]. In all of these models attention is a key feature, with skill postulated to grow with practice, facilitating a shift in awareness, described as a re-perceiving of, and potentially new relationship with 'reality' [132].

Attention is thought to comprise three distinct neural processing units [139]: 1) alerting, 2) orienting, and 3) conflict monitoring. Functional overlap with those brain areas associated with mindfulness meditation is apparent (Table 2.2)

Table 2.2 Attention: proposed subdivisions, functions and neural correlates

Aspect of attention	Function	Associated neural structures
1. 'Alerting'	i.e. 'readiness for an anticipated stimulus, including vigilance during prolonged tasks 'sustained attention'	PFC, intraparietal sulcus, locus correuleus, regions of the thalamus
2. 'Orienting'	i.e. selecting out specific aspects of experience upon which to focus 'selective attention'	dlPFC, mPFC, ACC, parietal cortex
3. 'Conflict monitoring'	i.e. the monitoring of conflict and its resolution. Sometimes called 'executive attention'	ACC

Research suggests that distinct components of the attentional system are active in expert meditators, and may be quite different to those in beginners, but Dickenson et al. [138] report that both complete beginners and experienced mindfulness meditators alike demonstrate improved emotion regulation. Expert meditators show increased acceptance towards distressing images, as compared with controls [140]. They also show evidence of enhanced executive attention and conflict monitoring, as compared to non-meditators, although stroop test results, which measure the ability to filter out irrelevant information, or interference, are not uniformly improved [132].

The ACC is believed to regulate executive attention and exert 'top-down' control over lower neuroaxis brain structures – hence, perhaps, the purported importance of *Intention* and *Attention* in the Shapiro et al. model for mindfulness [130]. Together

with the IC, the ACC is also involved in switching of attention, via disparate neural networks. Switching of attention is a key skill in mindfulness, where the wandering mind is identified and returned to the chosen object of attention [132]. Mind-wandering has been found to be positively associated with unhappiness [141].

ACC activity has been shown to be up-regulated both during and outwith regular meditation practice [142], with observed neuroplastic, i.e. structural and functional brain changes, also apparent. It has been suggested that enhanced ACC activity is an early phenomenon in meditation practice, diminishing as experience and skill grow [132]. Holzel et al. [132] suggest that changes in ACC activity are of potential clinical importance in conditions where executive control and function are impaired, such as Attention Deficit Hyperactivity Disorder (ADHD) and Bipolar Disorder (BPD).

Expert meditators show an enhanced orientating response, as do individuals following an eight-week MBSR training course [143]. There have also been improvements noted in those completing a month-long mindful retreat, and a three month-long 'Samatha' mindful breathing retreat. It remains debated as to how these reported benefits might manifest in the brain, but it seems likely that they act via ventral and dorsal sub-components of the attentional systems [132].

Attentional blink, or impairment of the time-dependent capacity to detect a salient object from a series of sequential stimuli, has been shown to improve following a three-month mindfulness retreat [132]. Increasingly it appears that the type of meditation practised will determine which components of the attentional system are active [132]. This may be important where an intervention aims to improve cognitive skills that allow an individual to orient preferentially towards, attach significance to/ or not, or to respond/ or not to stressful stimuli.

Tomasino et al. [144] have described how Buddhist and Hindu meditation styles utilise distinct neural systems. This may explain divergent, yet similar effects from the respective practices. Training these systems via mindful awareness, so that stress-inducing experiences can be preferentially engaged/disengaged-with, may hold benefit for people with MS. Grecucci et al. [128], and others, [130] relate this to a re-perceiving of the self, where prior 'fusion' of cognitive/ emotional states with an

enduring sense of self are prised apart and subsequently re-appraised in a more adaptive, and less stressful manner.

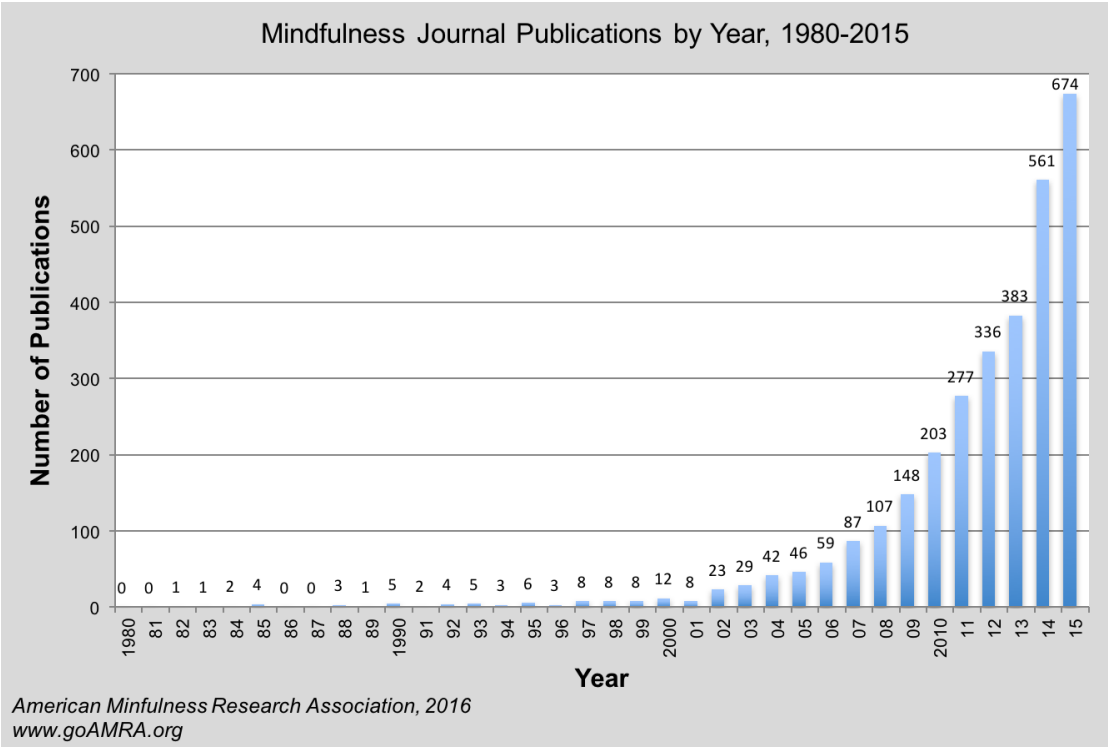
However, Farb et al. [133] suggest that mindful emotion regulation does not work via cognitive re-appraisal, or through any attempt to control one's emotional experience in a 'top-down' manner. Instead, they propose that it is through the preferential recruitment of non-conceptual, sensory/embodiment 'bottom-up' neural circuits, such as the thalamus, IC, and somatosensory cortex, that beneficial effects take place. Thus, a practitioner remains alert to the salience of present moment experience, without conceptual elaboration. This may limit cognitive elaboration of distressing experiences, and any associated negative evaluation of the self. When combined with an attitude of self-compassion, this approach might lead to increased tolerance for unpleasant emotions and a more adaptive response to moment-to-moment fluctuations in experience, translating into a distinct pattern of neural activity, with cumulative, and potentially lasting beneficial neuroplastic and functional effects [133].

'Trait' mindfulness describes an enduring mindful quality of awareness, which is inversely related to trait rumination, a key feature in depression and anxiety [145]. The development of trait mindfulness might help with the problematic 'negativity bias' commonly observed in depression and seen as a behavioural marker of depression vulnerability [146]. How mindfulness might achieve such ends is unclear. Possible mechanisms may include a shift towards positive reappraisal of SLEs [147], or non-reactivity to negative stimuli [148]. Goldin et al. [149] have proposed that when utilising MBSR amongst those with social anxiety disorder (SAD), it is through adopting a state of meta-awareness that mindfulness exerts beneficial effects i.e. by developing the conscious ability to observe current mental phenomena from a detached perspective [150].

2.8.1 Mindfulness as a healthcare intervention

Mindfulness was introduced into healthcare settings in the early 1980's by Jon Kabat-Zinn, primarily as a means of reducing stress in those with chronic illness. The first studies were among people with chronic pain and anxiety [151]. Over the last four decades, clinical research on the topic has risen exponentially (Figure 2.3).

Figure 2.3 Mindfulness journal publications by year, 1980-2015 [152].



Blue line indicates results from a search of the term 'mindfulness' in the ISI Web of Science database.

(Republished with permission from the American Mindfulness Research Association, 2015)

MBIs derive mainly from the eight-week long, group-based MBSR, conceived by Kabat-Zinn. This model has served as a template for further derivations, such as MBCT, an intervention specifically aimed at preventing depressive relapse [13, 153]. MBIs have influenced the development of other composite interventions, such as Acceptance and Commitment Therapy (ACT), and Dialectical Behavioural Therapy (DBT), but mindfulness does not form the 'core' of such therapies, which are described as largely directive [154].

In general, MBIs are considered 'safe' clinical interventions. Lustyk et al. [155] provide a helpful review of participant screening, safety, and researcher training. The authors point out that researchers should be aware of potential adverse effects, mental health concerns being foremost. Reported adverse events include enhanced feelings of anxiety and depression, and case reports of delusions, psychosis and mania. However, these have mostly been associated with intense, prolonged Vipassana retreats (an insight-orientated Buddhist meditation style [156]), which may also involve fasting, sensory deprivation, and altered sleep [155]. A physical health issue worth noting is a

potential for meditation to lower seizure threshold via decrease in serotonin, increase in glutamate, or via neuronal hypersynchrony, where large groups of neurones in the brain fire in synchrony. This effect has been reported with Transcendental Meditation (TM) [157], and is also seen in epilepsy [158]. This risk would be of primary concern in a known epileptic, but remains largely theoretical [155]

There have been a number of recent systematic reviews and meta-analyses on the use of mindfulness as a healthcare intervention. In 2003 Baer [154] published a conceptual and empirical review of controlled and observational studies of MBIs as clinical interventions (n=21), reporting beneficial effects across a range of medical and psychiatric conditions, with a weighted mean post-treatment ES of 0.59 (medium), which remained stable at follow-up. Clinically and statistically significant effects were largest for depression (ES 0.86), and lowest for pain (ES 0.31).

In 2004 Grossman et al. [14] reported a meta-analysis of published and unpublished observational and controlled studies (n=20 studies/1,605 participants) on the health benefits of MBSR, amongst individuals who were 'stressed', or had specific clinical conditions, such as anxiety, cancer, chronic pain, depression, or heart disease. A limitation was that findings were based solely on pre- post- intervention change effects. Amongst the controlled studies (n=771 participants), the authors reported an overall ES of 0.54 for improvements in mental health, and an ES of 0.53 for improvements in physical health. In the observational studies (n=894 participants), the ES was 0.50 for mental health, and for physical health 0.42. Results were supportive of improvements across a range of validated measures for anxiety, depression, coping, QOL, pain, and physical impairment.

In 2009 Mars and Abbey [17] carried out a systematic review on RCTs of MBIs as a healthcare intervention, including 22 studies in patients with medical and psychological conditions, such as depression, chronic pain, psoriasis, MS, cancer, heart disease, chronic fatigue syndrome (CFS), and substance misuse. They also included 'stressed' non-clinical populations. Findings highlighted positive health outcomes and decreases in psychological distress, with MBCT noted for effectiveness in recurrent depression. In the case of MS, the authors noted only methodological drawbacks and a small sample size limiting interpretation of findings in the single

study included. For other medical conditions, the authors found evidence of effectiveness for Mindfulness-Based Art Therapy (MB-ART) amongst female cancer patients, with reduced distress, improved vitality, social functioning, and QOL. They also found that in fibromyalgia patients, MBSR improved inner resilience, myalgic pain, and depression, whilst in heart disease, modified MBSR was associated with reduced respiratory rate, less anxiety, enhanced emotional expression and better coping. In psoriasis, MBSR was associated with faster skin healing. However, there were recurrent problems with methodological quality reported, such as small sample sizes, and a persistent lack of active control groups. Another consistent limitation was the widespread failure to include outcome measures for mindfulness, rendering inference somewhat problematical.

In 2010 Bohlmeijer et al. [16] conducted a meta-analysis examining the role of MBSR in the mental health of adults with chronic medical disease (cancer, CFS, chronic pain, fibromyalgia, and rheumatoid arthritis). This included eight RCTs. The meta-analysis reported beneficial effects in depression (ES 0.26), anxiety (ES 0.47; an effect which diminished to 0.24 when including only the highest quality studies), and psychological distress (ES 0.32). Cochrane criteria were used to assess quality, and subsequent guidelines were set out for empirically supported therapies. The authors noted a preponderance of female participants, and a tendency to focus upon the middle-older age groups. The meta-analysis employed tighter inclusion/exclusion criteria than Baer [154] or Grossman et al. [14], possibly explaining the smaller ESs.

Most recently in 2014, Goyal et al. [159] published a comprehensive and rigorous meta-analysis, examining the evidence for efficacy and comparative effectiveness of meditation programmes against active controls for improving psychological distress and wellbeing in adult clinical populations. MBIs were included. The authors assessed quality over four domains – consistency, directness, precision, and risk of bias. Forty-seven RCTs were included (n=3,515), covering populations with anxiety, depression, stress, chronic worry, insomnia, substance misuse, cancer, diabetes, heart disease, HIV infection, and pulmonary disease. Goyal et al. [159] reported low evidence for improved distress and mental–health related QOL, and insufficient evidence for stress related behaviours, such as disordered sleep, or weight management. More robust

end-point results for MBIs were evident for anxiety (ES 0.22 at 3-6 month follow-up) and depression (ES 0.23 at 3-6 month follow-up).

The MBI findings were across a diverse range of medical and psychiatric conditions. Goyal et al. [159] pointed out that meditation programmes in general were no better or worse than other active treatments, such as anti-depressants, exercise, or psychotherapy. They emphasise that such programmes are a viable and effective option against various aspects of psychological stress. The authors suggest that ESs for MBIs are comparable to antidepressants in primary care populations, with the ES for antidepressants quoted as 0.11 in mild-moderate depression, and 0.17 in those with severe depression. Limitations noted in the Goyal et al. [159] meta-analysis included that findings were limited to a primary care sample, with a potential floor effect, and thus small ESs. The methods used in the included studies were reported as inconsistent, with high levels of attrition, lack of blinding, and a lack of intention to treat (ITT) analyses. Interventions were diverse, varying in duration and instructor expertise. Although no study reported outright adverse events, potential harm reporting was generally poor, considered by only 9/47 studies.

2.9 Summary

This chapter has presented a background overview on MS epidemiology, aetiology, pathology, symptoms and comorbidity. Scotland has the highest incidence and prevalence of MS worldwide. MS is poorly understood. It is a stressful condition. Inflammation is a central feature in current models, but precise mechanisms remain unclear. Experimental evidence exists that stress can potentiate inflammation. Perceived stress is associated with increased mortality in multimorbid populations.

Stress raises the risk of depression in MS and impairs QOL. Psychological stress management is linked with diminished MS disease activity, but current evidence to support this finding is limited. Psychosocial interventions improve common MS symptoms of anxiety and depression, and improve QOL. More research is required to determine the optimal treatment.

Mindfulness is an ancient Oriental meditation technique adapted to Western medical settings, especially for managing stress in LTCs. How MBIs work is not fully understood. They are thought to operate via improving attention and emotion regulation skills, and by decreasing stress reactivity. Their role in MS is unclear.

Building upon this background, a rationale for studying MBIs in people with MS is:

1. Perceived stress can impair QOL in MS, increase vulnerability to depression, and possibly the risk of relapse;
2. Mental health comorbidity is likely to be high in MS;
3. MBIs have been shown to be effective in helping manage stress, treating anxiety and depression, and improving QOL in other LTCs;
4. People with MS value learning new skills to assist in stress management;
5. Effective stress management interventions for people with MS are limited.

The next chapter will outline and justify the general methods chosen to study the use of MBIs in people with MS in this thesis.

Chapter 3 General methods

3.1 Chapter overview

This chapter provides an overview of the methods used in this thesis. It starts by introducing the MRC guidance [19] for developing and evaluating complex interventions to improve health. The chapter is then split into sections, describing the steps from the MRC guidance [19] through which the researcher worked in an iterative manner, in order to answer the research questions set out in Chapter 1. This follows a sequence of discussing the methods chosen for:

1. Defining the population under study
2. Setting-out to identify systematically the existing evidence for MBIs in people with MS
3. Testing the feasibility of a standardised MBI in people with MS
4. Thematically analysing participant experiences from the MBI
5. Examining potential implementation issues
6. Thinking about next steps.

3.2 Developing and evaluating complex interventions in healthcare

As described in Chapter 1, the overarching aim of this thesis was to focus on the needs of people with MS, and in particular whether MBIs may help, with specific research objectives being to:

1. Measure comorbidity in people with MS in Scotland by characterising the number and type of conditions compared with the general population.
2. Delineate the existing evidence for effectiveness of MBIs in people with MS by carrying out a systematic review.
3. Test the feasibility and effects of conducting a RCT of a MBI for people with MS, and clarify whether a future definitive trial is currently merited.

4. Explore the perceptions and views of people with MS participating in a MBI (MBSR)
5. Examine the potential barriers to and facilitators of implementing a MBI for people with MS

The methods chosen for this task were based upon those suggested by the MRC guidance for developing and evaluating complex interventions to improve health [19, 160]. The MRC guidance [19] recommends that researchers consider a series of iterative, complementary, and interconnected steps when undertaking such an evaluation (Figure 3.1).

Figure 3.1 Developing and evaluating complex interventions to improve health

In this thesis, the application of these methods included the following:

1) Firstly, defining the population under study. This required developing an understanding of the epidemiology of multiple sclerosis, including the scope and extent of physical and mental health comorbidity in this population.

2) Secondly, defining the scope and extent to which MBIs have already been used in people with MS through carrying out a systematic review.
3) Thirdly, testing the feasibility of delivering a MBI to people with MS under trial conditions and assessing likely effectiveness in a future definitive trial.
4) Fourthly, determining stakeholder views on the accessibility and acceptability of a MBI for people with MS, by thematically analysing feedback from both course participants and course instructors.
5) Fifthly, determining the likely implementability of a MBI for people with MS via the application of an implementation theory to the qualitative findings from the thematic analysis.
6) Finally, thinking about the findings as a whole, what they show, and how this should be reported, but also in terms of what next steps may be necessary in order to create a MBI optimised for people with MS.

The rationale for choosing these methods and working through the steps from the MRC guidance [19] in the above order is outlined below.

The MRC guidance [19] suggests that in order to answer complex research questions, the use of multiple methodologies is likely to be required. In this context, diverse forms of data from various relevant sources can be compiled to generate a broader, more meaningful scope for an overall analysis. Complexity is increasingly seen as the norm in health services research. There is a general recognition of the need to look beyond simply measuring outcomes, and to link process evaluations, including delivery and organisation of health services, with clinical trial findings [161]. Such integrative mixed-methods approaches can increase confidence in the comprehensiveness and inclusiveness of findings [162]. ‘Mixed-methods’ research generally means taking into consideration both quantitative and qualitative research findings on a given topic. Including a variety of perspectives may intuitively make sense, but this approach is not entirely free from criticism. The main criticism is that quantitative and qualitative research approaches are based in different epistemological and ontological foundations, where epistemology refers to the nature of knowledge, where it comes from, and how it can be explored [163], and ontology refers to the

nature of the social world, what it comprises, and how its diverse aspects interact [163].

Traditionally, quantitative research is seen as having a 'positivistic' grounding, in that determinism (i.e. cause and effect) should be sought and identified as part of an 'objective' reality [164]. A criticism of this method is that it can be seen as 'reductionist'; seeking to test 'discrete' ideas and assumptions about reality, ultimately in pursuit of uncovering 'natural laws'. Thus, the use of numbers/ frequencies/ quantity i.e. statistics, is relied upon to determine 'truth' in the research hypothesis being tested [164]. A strength of this 'deductive' method is its inherent acknowledgement that any hypothesis should be modified in light of new information, and that the researcher remains 'objective' i.e. systematically seeks to remove sources of bias in his orientation and observation. A weakness with this approach is that it can actually by definition never 'prove' a hypothesis, only fail to reject it [164].

Qualitative methods, on the other hand, are a more recent development in research [162]. The approach differs from quantitative methods by proposing that, contrary to the 'positivist' perspective, there is no objective reality; that in fact what we refer to as 'reality' is actually a mere social construct i.e. 'constructivism', resulting from individual, or societal interpretation i.e. 'interpretivism' [164]. Whereas quantitative measures set out to answer specific research hypotheses, qualitative research may generate a new theory or patterns, which may only emerge during the research process [164]. Central to this theory is the idea of deriving 'meaning' in reality, from the subjective point of view of the individual. This can lead to multiple 'realities', these being more likely to emerge when the individual faces open-ended questions posed by a researcher using an 'inductive' approach [164]. The researcher then aims to clarify and make meaning of key emergent themes from participant feedback, being careful not to marginalise any minority groups, and remaining cautious about the role that his own background and assumptions may play in his interpretation and analysis.

Mixed methods are now commonly used in research [161], combing the strengths of both approaches. That is why they have been chosen to help address the complex questions posed in this thesis.

3.2.1 Defining the population to be studied and the rationale for the intervention.

Scotland is known to have the highest MS prevalence rates worldwide (see Chapter 2 for a more detailed discussion). However, at the time of starting this thesis, there were no existing population-based studies on comorbidity amongst people with MS in Scotland. The first part of the research in this thesis was thus based in epidemiology, and focused specifically on answering the question as to the level and extent of comorbidity in people with MS compared to the general population.

In order to delineate the prevalence of comorbid diseases amongst people with MS in Scotland, a nationally representative primary care database from Scotland was accessed. This involved undertaking a secondary analysis of the database, which had been developed as part of a national programme for research into multimorbidity [165]. The database was cross-sectional, measuring the prevalence of comorbidities over a defined single time period, as a 'snapshot' [166]. Full details of this process are described in Chapter 4.

Epidemiology can be defined as: '*how often diseases occur in different groups of people and why*' [166]. It is mainly concerned with groups of people and can be used to measure outcomes in 'at risk' populations, where a person with the condition represents a 'case'. It can be very useful in planning treatment strategies in people with specified medical conditions [166]. Most epidemiological studies are observational, comparing groups likely to differ in many ways, such as in age, sex, and SES. Such variables can act as confounding factors when appraising epidemiological data, in that certain conditions may be more likely to occur in older individuals, females versus males, or in the less affluent, and thus may potentially obscure relationships between exposure to certain conditions and the presence of a disease. However, such confounders can be statistically controlled for in quantitative analysis of such data in a number of ways, allowing closer scrutiny and focus on the variables of interest. For example, by isolating a 'dependent' variable, one can home in on the relative contributions other variables make to the prevalence of other comorbid conditions in people with MS. By controlling for age, sex, and SES, differences in the prevalence of depression can be sought between people with MS

and those unaffected, without these demographic variables exerting an otherwise 'hidden' influence on the results generated [166].

'Prevalence' is an epidemiological term referring to '*the proportion of a population that are cases at a point in time*' and for rarer diseases like MS is thought to be a better measure than 'incidence', or '*the rate at which new cases occur in a population during a specified period*', due to the relatively low numbers reported annually [166].

Population-based studies tend to be most useful in epidemiology, giving a more stable risk estimate [166]. Population-based data is particularly useful as a means of controlling for random variability that may occur in small samples, and thus allows a greater degree of confidence that findings can be applied to research design and assumptions. A notable limitation is that cross-sectional data cannot be used to delineate definitive causal relationships, and observed associations thus require cautious interpretation [166].

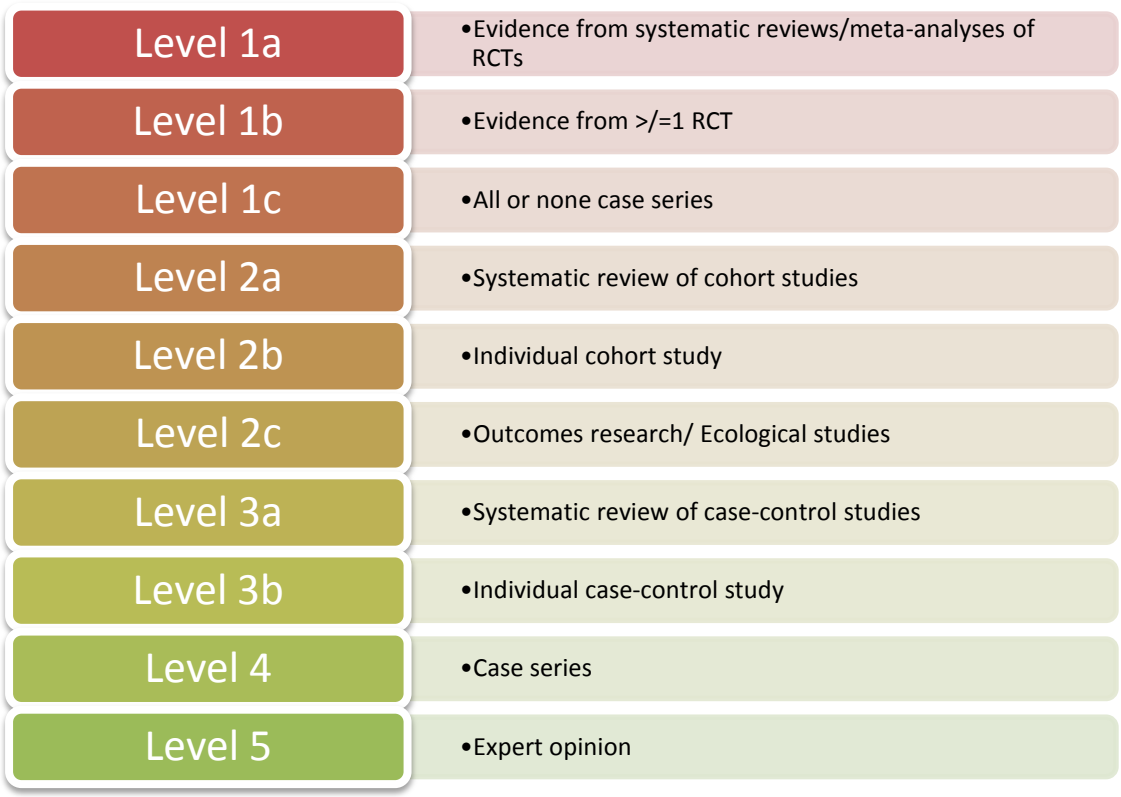
In the cross-sectional database study described in Chapter 4, odds ratios (ORs) with 95% confidence intervals (95% CI) were used as a means of describing the analysis of the data. These were adjusted for important potential confounders, including age, sex, and SES, and are reported for those with MS versus those without. ORs describe the odds of a defined event taking place in one group divided by the odds of it happening in another group [167]. ORs are useful when comparing individuals with a particular condition i.e. cases of people with MS, with MS-free 'controls'. A ratio of 1 represents no difference. A ratio greater than 1 indicates increased odds of an event taking place; and a value of less than 1 indicates decreased odds. ORs are usually accompanied by 95% confidence intervals, and if the range of values in the confidence interval does not cross zero then it implies a statistically significant result [167]. 95% CIs represent the range of values within which we can assume that 95% of the true population does in fact lie, thus boosting external validity. It has certain advantages over significance testing, i.e. 'p' values', in that it allows us to see relationships between different variables, and also in that 'p' values can vary widely, making subsequent predictions regarding effects in complex scenarios very challenging [167, 168]. In epidemiology, 'p' values are used to determine if differences between two populations of interest differ in terms of distribution, and

allow a calculation of the probability as to whether a positive result occurred by chance. 'P' values are conventionally set as 'significant' if less than 0.05, or 5% i.e. there is less than a one in 20 probability of occurring by chance alone. Some critics argue that 'p' values are quite arbitrary, can vary widely on repeated testing, and are thus made more useful if combined with confidence intervals [167, 168].

3.2.2 Defining the scope and extent to which MBIs have already been used in people with MS – is there existing evidence for effectiveness?

In the Evidence-Based Medicine (EBM) paradigm of '*Hierarchy of Evidence*', systematic reviews and meta-analyses of RCTs are seen as the 'gold standard', or representative of 'Level 1a evidence', meaning that results from such studies can be taken as the best available evidence on a given subject [169] (Figure 3.2).

Figure 3.2 Oxford Centre for Evidence-Based Medicine 'Hierarchy of Evidence' [169]



In this thesis, a systematic review was undertaken, setting out to delineate the scope and extent of evidence that exists for the effectiveness of MBIs amongst people with MS. The systematic review primarily examined for the effects of MBIs on perceived

stress as the primary outcome, but also for a variety of other relevant secondary outcomes such as mental health, physical health, QOL, and cost-effectiveness in people with MS. The systematic review, given its rigour and depth of searching, also allowed the researcher to identify any important gaps in knowledge about the use of MBIs in people with MS. Full details of the systematic review process and findings are described in Chapter 5.

A systematic review is a research method that allows the researcher to search the literature, both academic and 'grey', systematically and comprehensively. It is done in order to answer a specific research question, or set of questions where uncertainty exists, before distilling this information into a manageable and accessible format [170]. A systematic review starts by setting a focused clinical question in a specific population. In this case, the research question was focused on what evidence existed from RCTs and/or controlled trials for the effectiveness of MBIs at improving perceived stress in people with MS.

In a systematic review, there are pre-defined inclusion criteria, and explicit research methods are employed throughout to identify and select appropriate studies before critically assessing the findings. This process includes scrutinising the study types, i.e. RCTs and/or controlled trials, the population characteristics/ demographics, the intervention designs i.e. 'type' of MBI, and the range of outcomes reported, including those of both primary and secondary importance for the purposes of the review [171].

The review process is transparent and should be reproducible, being guided by a prospective, peer-reviewed protocol, designed partly to reduce any latent reviewer and/or publication bias [171]. The search is often aided by input from an information scientist, employing carefully selected bibliographic key words, along with Boolean operators, Medical Subject Heading (MeSH) descriptors, and predefined delimiters, such as language, publication dates, human subjects etc. These methods are applied in order to refine the search towards finding and retrieving relevant articles from major electronic databases, which are compiled and indexed around standard bibliographic convention [170]. This approach can then be further enhanced by hand searching and scrutiny of reference lists from identified studies [170].

Data extraction and quality assessment are done systematically [172], via a rigorous process involving crosschecking by a team of reviewers, looking specifically at such items as randomisation, blinding, and attrition. In this case, a pre-defined data-extraction form was used, previously developed for a systematic review on the effectiveness of MBIs amongst people who had suffered from a stroke. The form was completed on all selected studies by two independent reviewers i.e. the researcher, and an experienced systematic reviewer. Findings were compared and adjudicated over by a further reviewer and senior academic, the researcher's supervisor (Professor Stewart Mercer - SM).

Systematic review results may subsequently be subject to further statistical scrutiny in a meta-analysis across studies, where heterogeneity can be assessed i.e. testing the probability as to whether differences between the study findings are likely due to chance alone [173]. Minimum reporting standards for systematic reviews of RCTs exist, for example the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), an approach which has itself been shown via systematic review to improve evidence reporting [174]. For meta-analysis, results can only be combined where studies measure the same outcomes, and in the case where they do not, a narrative review may be a more appropriate method of reporting [171]. That proved to be the case in this present study.

The reason for preferentially seeking out RCTs in systematic reviews is that randomisation of study participants reduces research bias by controlling for potential confounding by other variables, such as age, sex, SES. The randomisation process theoretically evens out the distribution of such variables between the groups into which participants are allocated in their respective studies [169]. However, RCTs do not provide much information on how interventions work on individuals or collectively and thus the MRC guidance [19] suggests that they should not be viewed in isolation, but interpreted in conjunction with other important sources of evidence.

For the reasons outlined above, a systematic review is a persuasive tool to inform policy and practise in a climate of evidence-based decision-making [170].

3.2.3 Testing the feasibility of delivering a MBI to people with MS under trial conditions.

This research question related to the feasibility of being able to replicate and test the intervention of interest in the population of interest, which in this case was a MBI amongst people with MS. In this thesis, MBSR was tested in a pragmatic feasibility RCT. This process will be covered in full detail in Chapter 6.

As discussed in Chapter 2, MBIs have been applied as a treatment strategy in a wide range of LTCs, and have demonstrated effectiveness in a number of these contexts. This did not automatically mean that these same effects would be observed in people with MS, but it did suggest that it would be worth investigating in a MS patient group and prudent to collect a range of outcomes measures of relevance to this particular population. Thus, feasibility work was required.

Piloting and feasibility testing aims to reduce the number of studies undermined by issues that could have been anticipated by appropriate developmental work, such as poor recruitment, high attrition, and small ESs [19]. 'Feasibility' is about testing trial procedures and methods and may thus precede a 'pilot study', which is often characterised as a scale model for a definitive phase-3 trial, when the researchers are happy with the intervention and are not expecting any further modifications. It is worth noting, however, that this sequence and set of definitions are not uniformly followed in the literature, and another conceptualisation might be where research seeks first to 'pilot' and optimise an intervention, before then testing in a feasibility RCT [175].

A rigorously conducted RCT is widely regarded as the best method for evaluating interventions to improve healthcare [176]. Therefore, a RCT was chosen as the experimental method in this study, primarily for testing feasibility, but also for investigating likely treatment effects on relevant outcome measures. The MRC guidance [19] reminds researchers to remain aware that failure to demonstrate effect in this setting may occur for numerous reasons, that variation amongst individuals is likely, indeed the norm. At this stage the MRC guidance [19] recommends that any

control group should on balance receive 'usual treatment', since using an 'active' control at this point may serve to confuse/confound the interpretation of findings.

The MRC guidance [19] suggests that researchers should ideally consider a RCT study design when testing a novel intervention, as this is the best method to guard against selection bias and sample variability. However, although randomisation is desirable, it is not essential. Arguably, when an intervention is not yet optimised for a specific population, a more suitable alternative can be to test feasibility in a pre- post- study. Potential advantages include greater flexibility to modify the intervention in real time and lower costs [19]. In this study, a RCT was chosen in favour of a pre- post- study because MBSR had previously been used successfully in ambulant people with MS [177], the timescale for the PhD project was limited, a wait-list control design might allow optimisation changes to a planned second iteration of MBSR to those initially allocated to 'control', it would allow the generation of effect estimates for a definitive study, and it was clear that RCT procedures would eventually require testing for feasibility and their acceptability to people with MS in this context. Patient and public involvement (PPI) through a grant application made to the UK Multiple Sclerosis Society (MSS) suggested that this decision was justifiable to people with MS, albeit from an admittedly small sample (n=3) (Appendix A).

Fidelity is an important and often overlooked consideration when testing behavioural interventions [178]. The MRC guidance [19] suggests that assessing intervention variability is an important issue, particularly in the case of a study involving multiple sites. However, in this study, a single site was chosen for pragmatic reasons, and the MBI facilitators remained the same throughout. From a pragmatic perspective, although MBSR is a manualised MBI, minor modifications do occur in normal practice, based largely upon idiosyncrasies that may present with each new group of participants [13].

Testing feasibility and performing piloting work was deemed necessary in this study when considering that the standard package of MBSR might not be optimal for people with MS. The main feasibility outcomes assessed how feasible it was to recruit, retain, and follow-up people with MS to take part in a MBSR intervention, as well as the likely effectiveness of the intervention. This comprehensive approach provided

insight into stakeholder interest, engagement, and sustained involvement i.e. whether people with MS were willing to attend the MBSR sessions or remain on a waiting list and continue to complete relevant outcome measures for the duration of the study. In addition to testing the feasibility of trial procedures, exploration of likely treatment effects provided useful data to help determine the required sample size for a phase-3 definitive trial. Important elements included confidence about effect sizes and variability.

The MRC guidance [19] suggests that questions of feasibility, accessibility, acceptability, adherence, and intervention delivery should ideally be addressed before ever proceeding to a phase-3 trial. If such elements are lacking, then it becomes questionable whether the intervention can actually be delivered as intended. In terms of replicability, the MRC guidance [19] emphasises the importance of being able to describe the intervention fully from the outset. In this regard, MBSR was a manualised and replicable MBI [13], previously having been widely used across a variety of other relevant LTCs [16, 17].

MBSR was originally designed to help people with LTCs cope with stress and chronic pain [151]. It was not designed as a 'cure', but as a means of helping people to accept and live with their condition(s) in a more adaptive manner [13]. As noted in Chapter 2, MS is a LTC with high levels of comorbidity, that comes with inherent uncertainty surrounding disease relapse and/or progression [20], and various social and role challenges, all of which can be stressful and can impair QOL [3, 179, 180]. The primary purpose of the intervention in this context was to provide a mindfulness-based stress management programme to diminish perceived stress and improve QOL.

The MRC guidance [19] suggests that when investigating a new intervention/context, a range of outcome measures should be sought, instead of focusing simply on one primary measure. Validated measures can give an indication of likely effects from the intervention, although causal pathways can remain very difficult to pick apart on this level [19]. In this study, qualitative semi-structured interviews from participants were also collected, detailing their experience of the intervention and its perceived effects, or lack thereof, being used to complement and augment quantitative measures – (this will be covered in more detail in section 4, below).

The MRC guidance suggests that quantitative outcome measures should be both ‘valid’, and ‘reliable’ [19]. In quantitative research, ‘validity’ means the degree to which the tool actually measures the phenomenon or outcome of interest [181]. Similarly, ‘reliability’ refers to ‘precision’ and the extent to which repeated measurements of a phenomenon are consistent, dependable, and reproducible [181]. Thus, this programme of work selected a range outcome measures addressing perceived stress, QOL, common MS symptoms, and measures of mindfulness that have been shown to be both valid and reliable in MS populations, or related conditions. Chapter 6 reports the full details of the outcome measures chosen, including their basic psychometric properties.

The justification for choosing perceived stress as a primary outcome measure was that stress is known to be common in people with MS, it can increase the likelihood of developing depression in MS, reduce QOL, and potentially exacerbate disease activity [6, 8, 182] (see Chapter 2 for a fuller discussion on these points). The Perceived Stress Scale-10 (PSS-10) was chosen as a widely used and validated measure that covers both negative and positive aspects of stress appraisal and coping [183-185], with the PSS-10 having the most favourable psychometric properties in people with MS compared with the shorter four-item or longer 14-item versions [186].

A generic QOL measure was chosen as a second primary outcome, based on recognition that QOL is often severely diminished in people with MS [59, 73]. The EQ-5D-5L was selected as a widely used and validated generic measure that has been recommended for people with MS [187]. It is a short measure, and was thus attractive in helping to keep participant measure completion burden to a minimum. The EQ-5D-5L has been widely validated across the world, with weighted data available for UK populations, and can also contribute to an analysis of cost-effectiveness [188].

Cost-effectiveness is another important consideration when assessing novel interventions. Such information can be useful for health service commissioning, and is recommended by the MRC guidance [19]. An evaluation of economic value can contribute to decisions regarding implementation and sustainability, and whether an intervention is worth long-term investment. In practice, cost-effectiveness cannot be reliably determined in a small-scale study such as this [189], but it did make sense to

consider it at the feasibility stage [19]. Due to the small scale of this feasibility study and associated resource constraints, a decision was made by the researcher and his supervisors not to conduct a formal assessment of cost-effectiveness.

Secondary outcome measures sought to assess the impact of mindfulness training on common MS symptoms and comorbid conditions. After considering of a range of options [187, 190], a MS-specific composite measure, the Multiple Sclerosis Quality of Life Inventory (MSQLI), was chosen as it covered several relevant domains including fatigue, mood, cognitive function, social support, vision, pain, bowel, bladder and sexual function [191]. Although it had not been used previously in UK populations, it had been validated in North American MS populations across a range of ages, including those with cognitive impairment [192, 193].

In addition, given the putative links between impaired emotion regulation, stress, depression, and diminished QOL in people with MS (covered in chapter 2), a measure of emotional lability was also included. At the time of designing the trial protocol, the researcher was unable to identify any validated MS-specific measure and thus the Emotional Lability Questionnaire (ELQ) was selected for use [194]. The ELQ is a validated measure [195] that was originally designed for people with Motor Neurone Disease (MND), a condition with similar cognitive and emotional symptoms to those commonly seen in people with MS [196].

Further secondary patient report outcomes included measures of mindfulness and self-compassion. These measures were included as ‘process’ measures i.e. seeking to determine whether these constructs showed improved scores following mindfulness training versus controls. The development of mindfulness and self-compassion have both been described as key theoretical facets as to how/why MBIs exert beneficial effects in people with LTCs [13, 197]. A wide range of measures for mindfulness have been described, their psychometric properties recently examined via a systematic review [198]. Park et al. [198] conclude that those measures with the most supportive psychometric data include the Five-Facet Mindfulness Questionnaire (FFMQ) and the Mindful Attention Awareness Scale (MAAS). The FFMQ had previously been used to assess mindfulness in cross-sectional studies of people with MS [199, 200], but neither measure had been used in longitudinal studies. In this study, the MAAS was

chosen, as it was the most widely studied and validated measure, with supportive quality ratings for most psychometric measures, and in contrast to the FFMQ, measures mindfulness as a unified construct [198]. At the time of writing the protocol for the RCT the construct of self-compassion had never been studied in MS populations. The Self-Compassion Scale-short form (SCS-sf) was chosen as a concise, validated and responsive measure that has been used to assess the construct across a wide range of LTCs [201, 202].

The quantitative evaluation in the feasibility RCT examined between-group differences on baseline and outcome measures i.e. those allocated to MBSR, versus those in a control group. In this scenario, 't' tests were used to compare the means between the groups. T tests are a 'parametric' test, requiring normally distributed data, testing the probability for the 'null hypothesis' i.e. that two sample groups come from a population having the same value for the mean [167]. For non-normally distributed data, Chi squared (X^2) tests were used instead. X^2 is a 'parametric' hypothesis test of the association between two categorical variables i.e. different categories of the same thing, such as eye colour, gender etc, looking for differences between expected, and actual frequencies. If the null hypothesis is true, X^2 will equal zero. However, if a difference between the groups does exist, then the bigger the difference, the greater the value for X^2. A 'p' value usually accompanies a X^2 as a means of demonstrating significance [167].

In order to explore further the relationship between groups in the feasibility RCT, regression analyses were used as a means of defining the relationships between variables, one of which was 'dependent' upon the other i.e. precedes, or influences its value. Regression analyses can be either 'linear', where a 'best fit' line is drawn through a set of values in attempt to simplify the relationship between them, or it can be 'logistic', where the dependent variable is binary and only able to take one of two categories. Logistic regression can be used to predict binary outcomes, such as whether a patient has an outcome e.g. a disease, or not. Linear regression is used to assess how sets of data relate to one and other [167].

As a feasibility study, the RCT in this thesis was not powered to detect effectiveness, but it was able to give an indication of likely effects across a range of outcome

measures. The RCT analyses reported ESs for outcome measures, which are a measure of the magnitude and practical significance of differences observed in treatment effects on outcome measures between the two groups [167, 203]. Over 40 different methods are described for measuring effect sizes, but Vacha-Haase and Thompson [203] describe three major classes:

1. The first class assess standardised difference in effect sizes, which has the advantage of allowing comparison across heterogeneous outcomes in a broad literature such as exists in medicine. These are calculated by subtracting post-test mean of the control group from the experimental group and dividing by the entire population standard deviation (Cohen's 'd'). An alternative is to use the standard deviation from only the control group data (Glass's 'delta'), which may improve precision where a researcher can confidently determine that an intervention has not impacted on the control group's standard deviation. Delta may also be preferable when there is a large control group sample size, so that combining the intervention and control group data does little to improve precision, or when the intervention and control groups are very different from one and other [203].
2. The second class of techniques are termed 'variance-accounted-for indices', are associated with general linear statistical models, rely on correlations, and can allow sophisticated statistical calculations with 'weight' applied to variables and partitioning to determine which variables contributed what to the outcome effect size. However, effect sizes from such models can be difficult to interpret regarding their practical significance [203].
3. The third class are termed 'corrected effect sizes', so named as they 'correct' for sampling error variance in the sample data, such as effect characteristics unique to the given sample, thus preventing erroneously inflated effect estimates due to small sample size, or a large number of measured variables. Theoretically, corrected effect sizes may be most accurate, but debate exists as to at what levels sample size, variable number, and population effect sizes should be corrected [203].

Vacha-Haase and Thompson [203] suggest that when reporting effect sizes, researchers should consider:

1. Which types of effect size are being reported? This matters, as different expressions exist that are not directly reciprocal, although conversion formulae can be used in most cases.
2. What assumptions and limitations does each method have?
3. Confidence intervals should also be reported, which allow an estimate of precision, and aid in comparison across a study or across multiple studies, such as in meta-analysis.

In this study, standardised effect sizes using Cohen's 'd' were chosen to allow practical comparison with findings in the related literature where they are commonly reported. The use of Delta was not felt to be required, given that baseline differences between the groups were minimal, and thus this technique was unlikely to improve precision. Cohen's 'd' scores were thus calculated by dividing the observed treatment effects for a given variable i.e. differences between the treatment and control groups, by the standard deviation for the variable of interest for the group as a whole [204]. Effect sizes with confidence intervals have the advantage over significance testing, which cannot evaluate replicability. Instead, by using effect sizes and confidence intervals, results from multiple studies can be compared to determine whether results are consistent with other published data in the field, or stand out as anomalous [203].

Where beneficial effects were observed, their values may be used later to inform 'power', meaning the probability that a future study will observe a statistically significant difference between treatment groups, when one truly exists. Where the study failed to show effects, further exploration as to how/why this occurred could be undertaken through the linked process evaluation (covered in more detail in section 4, below). Assessing the magnitude and variability of effects in this feasibility study meant that this data would be available to guide sample size likely to be required for a future phase-3 trial.

The Consolidated Criteria of Reporting Trials (CONSORT) guidance is widely acknowledged and accepted as a 'gold-standard' method of reporting on RCTs [176], and was utilised in this study (see Chapter 6 for the CONSORT reporting checklist and diagram applied to this study). The CONSORT group suggest that poor reporting can seriously hamper interpretation of study findings, and the checklist is designed to

guard against this [176]. The guidance seeks to standardise reporting, to include clear and structured information in RCTs, with:

- A title that clearly identifies the study as a RCT, with an accompanying abstract delineating design, methods, results and conclusions
- An introduction highlighting scientific rationale, with specific aims and objectives for the trial
- Clearly described methods about study design, participants, the intervention, outcomes, sample size, randomisation, blinding, and statistical methods
- Results highlighting participant flow, recruitment, baseline data, numbers analysed, outcomes and estimation, ancillary analyses, and harms
- Discussion of limitations, interpretation of findings and consideration of their generalisability
- Details regarding registration of the trial in a recognised registry, along with pre-defined protocol, and funding source(s).

The MRC guidance [19] recommends that statistical advice be sought early in the course of developing and evaluating complex interventions, and this was the case in this current study, both for analyses and results reporting, with input and supervision from staff in the Robertson Centre for Biostatistics (RCB), University of Glasgow (Miss Suzanne Llyod and Dr. Alex McConnachie).

3.2.4 Determining stakeholder views on the accessibility and acceptability of a MBI for people with MS

In mixed-methods research, quantitative outcome measures can be supplemented through the addition of qualitative data. In the RCT in this study, a parallel process evaluation was carried out involving semi-structured stakeholder interviews. An advantage of including a process evaluation was that it could provide valuable information to test assumptions about the research hypotheses, the intervention, or the outcome measures chosen [205].

The intention in this study was to examine participant views on their experiences of MBSR. The MRC guidance [19] suggests that this process should be theory-informed. In this study, a thematic analysis was employed first to capture emergent, unabridged participant views. Following this, Normalisation Process Theory (NPT) [206, 207], was used as a theoretical 'lens' for scrutinising the themes arising from the thematic analysis. These methods are explained in more detail below and Section 5 will cover the use of NPT. Chapter 7 then gives full details of the qualitative research process.

3.2.4.1 Measuring quality in qualitative research

The scope of qualitative research methodology is extensive and varied. When selecting methods for a study such as this, quality assurance should feature as a distinct consideration from an early stage. Mays and Pope (2000) suggest that in order to demonstrate rigour, qualitative research should be subject to an assessment of its quality via two broad criteria, namely relevance and validity. The approach used should be systematic, but also reflexive in its design, data collection, interpretation, and dissemination [208]. Hammersley [209] has suggested that any theoretical claims coming from a qualitative research study must be consistent with the data, that the data source from which it originates should be credible and valid, that an analysis should consider the external validity of the findings, that the research process should be transparent and reproducible, and that its interpretation should be reflexive. However, Mays and Pope [208] also suggest that qualitative research methods should be malleable, when considering the distinctive goals in each study.

Validity can be assessed via [208]:

1) Triangulation, where findings from a qualitative analysis may be compared against other sources, such as those from the RCT;
2) Respondent validation, where respondents' review the researcher's account;
3) Provision of a clear account of the research process;
4) Reflexivity, where the researcher reflects on how, during the research process, the researcher may himself influence interpretation and analysis of the data;

5) Attention to negative cases or 'deviant case analysis', where emergent themes and/or theories are tested against the original data; and
6) 'Fair-dealing', where a clear attempt is made to include as broad a range of participant views as possible, not focusing explicitly on single viewpoints as representative of the group as a whole.

Relevance can be assessed by whether/how findings add to existing knowledge, including the generalisability of findings. The amount of detail included in the account can serve as a means whereby a reader can make a critical assessment regarding wider relevance – thus the sample from which data is drawn should be as broad, and as representative as possible [208].

Smith and Firth [210] describe three broad approaches to qualitative data analysis:

1) Models which examine the use and meaning of language – 'socio-linguistic methods' – such as Discourse Analysis
2) Models concerned with developing new theories, such as Grounded Theory
3) Models that set out to delineate and interpret participant views, such as Thematic Analysis.

Whichever method is chosen, the researcher is encouraged to make every attempt to adopt a rigorous, unbiased, and 'open' approach to data analysis.

In this study, qualitative data was gathered from semi-structured interviews with MBSR participants and instructors. Smith and Firth [210] suggest that analysis of any qualitative research interview data should involve the following steps:

- Interview transcription
- Becoming immersed in the data
- Developing a coding system
- Linking codes into higher order categories, which may or may not lead to the subsequent development of new theory

Thematic analysis is an interpretative technique that can bring to light unabridged participant descriptions of their experience of MBSR, the analysis seeking to elicit and describe the nature of any underlying patterns that exist in the data. Thematic analysis allows for rich accounts from research participants to emerge via an iterative process of data coverage and analysis. In thematic analysis, no explicit attempt is made to interpret findings in their element, but the accumulation of recurrent patterns and themes can become obvious via the wide coverage of the data that this technique allows [210]. No attempt need be made to generate new theory, and phenomena unearthed can be applied across varied epistemological and ontological perspectives.

The thematic analysis in this thesis was also guided by the Framework Approach [211]. The framework approach augmented and bolstered the rigour of the thematic analysis, by ensuring the iterative, yet non-linear process was systematic, transparent, and open to audit, whereby the linkages between different stages of the process and the emergent themes generated could subsequently be 'laid bare' and open to critical scrutiny [211] (see Chapter 7 for full details of the thematic analysis).

3.2.5 Determining the implementability of a MBI for people with MS.

The MRC guidance [19] recommends that implementation should feature in the researcher's thoughts from an early stage, considering potential barriers and facilitators to the uptake and engagement with the intervention, before moving on to a definitive phase-3 study. The MRC guidance [19] suggests that this should take account of views from the broad range of stakeholders likely to be involved in any eventual use of the intervention.

The MRC guidance [19] suggests that implementation may include, amongst other things, dissemination, or publication of findings, surveillance, monitoring, and long-term follow-up. Implementation necessarily involves decision makers, and as such, study findings and results have to be easily accessible and interpretable, with coherent recommendations presented in sufficient detail. The MRC guidance [19] suggests that costs, benefits, and harms are all necessary pieces of information and that policy

makers should have easy access to these when making more general recommendations for implementation.

Moving the study from the research setting into more general implementation in routine clinical practice is unlikely to be a straightforward process. The MRC guidance [19] suggests that an understanding and description of any necessary behavioral changes may be required. Furthermore, the guidance suggests that even if an intervention becomes established in routine practice i.e. 'normalised', evaluation should continue at that point and beyond, with care being taken to assess for any longer-term effects that may not have been identifiable earlier in the evaluation. This highlights again the benefits associated with the iterative nature of the process, and the importance of good planning.

Nilson [212] defines implementation science as: '*the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice to improve the quality and effectiveness of health services and care*'. In this context, implementation is seen as part of a continuum of '*diffusion-dissemination-implementation*', where diffusion is the passive spread of innovative practices, dissemination active, and implementation about how new practices become integrated in novel contexts/settings.

The MRC guidance [19] suggests that implementation should be theory-based, and Nilsen [212] warns that when implementation research has a poor theoretical basis, understanding how/why processes succeed or fail is hampered. Having limited insight into what factors impede, or promote successful implementation limits the likelihood of future success [212]. Theories can have an advantage over the simple application of 'common-sense' or an 'educated guess', in that theories are explicit, can be openly scrutinised, used/not depending on applicability to the research question(s) at hand, and provide a context for findings. On the other hand, care has to be taken not to apply theory blindly, to 'shoe-horn' data to fit where really it does not, and rigid application of theory may serve to hinder the development of new knowledge [212].

Nilsen [212] suggests that implementation theories cover three broad domains:

1) Process models – guiding the translation of research into practice
2) Implementation theories, classic theories, and determinant frameworks – which aim to understand and/or explain what variables impact on implementation outcomes
3) Evaluation frameworks – which are designed to assess implementation.

In this thesis, NPT was chosen for the parallel process evaluation as a means of assessing implementability. The reasons for choosing NPT were that it was a research tool designed for studying the implementation of complex interventions in healthcare settings [213], it was suggested by the MRC guidance [19] as an appropriate implementation tool in this context, it had been widely studied in this context, and one of the researcher's supervisors (Professor Frances Mair) was an expert in its use.

NPT is a sociologically-derived action theory for analysing how social processes i.e. complex interventions are enacted by people implementing new practices [206]. It can be used in feasibility work, mapping the individual, collective, and resource challenges that may be encountered introducing novel complex interventions [206].

For any new complex intervention, May [214] suggests that health service decision makers require to appraise and assess its '*workability, clinical- and cost-effectiveness*', and also its ability to '*integrate*' into existing/new paradigms and professional practice, such as service delivery, organisation, and quality improvement. NPT sets out to delineate facilitators and barriers to the process of implementation, and also allows for estimations regarding likely incorporation into routine practice (see Chapter 7 for full details of the NPT analysis).

NPT proposes that four key domains of behavior should be assessed [214]:

1) Coherence - This refers to sense-making amongst stakeholders, individually and collectively, when charged with operationalising a new set of practices
2) Cognitive participation - This assesses the relational work that stakeholders undertake to create and sustain a community of practice around a new intervention

3) Collective action – This refers to the operational work that stakeholders have to do in order to enact the practices of the new intervention
4) Reflexive monitoring – This refers to ongoing appraisal and assessment of how the new practices impact on the stakeholders, and those around them.

Combining a NPT analysis with findings from the thematic analysis had advantages [206], as the two approaches addressed different aspects of the qualitative data. Using NPT was about making sense of collective and distributed patterns of work, and specifically *not* about individual intentions and perceptions [206]. In contrast, thematic analysis was about exploring individual perspectives [210]. Further, thematic analysis was seen as a means to extract participant views directly from participants in a format minimally removed from their raw expression, whilst NPT was applied as an integrative theoretical framework to inform conceptualisation of the thematically analysed data [206].

NPT can be applied flexibly to managing qualitative data, or modified in vivo, to suit the ecology of the data and context of the intervention setting [206]. It is not a prescriptive protocol, and can be used in both 'positivist' and 'constructivist' paradigms, which is useful in mixed-methods research [206]. NPT can be used at various points in the research process. In this thesis, NPT was used initially to inform the design of the semi-structured interview questions, then again at a later stage, as a theoretical 'lens' through which to conceptualise the emergent themes. During this process the researcher had to keep in mind the possibility that the data might not fit neatly under a NPT 'lens'. To guard against this, the thematic analysis was conducted first, and then the initial analysis was conceptualised using NPT. In this way inappropriate 'shoehorning' of qualitative data was avoided and the researcher could incorporate data that might not fall within the NPT framework.

NPT suggests that successful implementation depends upon coherent and organised, dynamic and contingent interactions between stakeholders, over time [215]. The term 'interactional workability' describes how well individuals come together to make the intervention work. 'Relational integration' describes how a complex intervention becomes translated from theory into practice, through individual and collective responsibility being assumed by stakeholders to drive forward its successful integration. 'Skill-set workability' assesses how the necessary work required to

implement the intervention is divided up amongst the stakeholders, and can thus be useful for identifying gaps in the skill set. 'Contextual integration' describes how well the intervention fits into the context in which it is being implemented, and includes consideration of resourcing and on-going evaluation.

3.2.6 Interpreting and reporting findings, and thinking about next steps

The MRC guidance [19] suggests that optimising an intervention is an iterative process of testing an approach, reviewing process outcomes, and modifying on the basis of these (see Chapter 8 for full details of how findings from the five previous research steps could be used to optimise MBSR for people with MS).

Campbell et al. [216] suggest the following as key tasks in optimisation work:

- Identification of the key processes and outcomes
- Identification of mechanisms that lead to improved outcomes
- Identification of possible rate-limiting steps/barriers preventing intervention
- Quantification of potential benefit and estimated likely ESs
- Refining the target group, based on the likelihood of responding
- Defining the optimum combination of intervention content and dose.

Important pragmatic considerations in optimisation work relate to 'internal validity'. For example, making necessary modifications to an intervention, even if 'minor', can raise important questions about whether the intervention is still a MBI. Similarly, from the perspective of 'external validity', important questions have to be asked about reproducibility e.g. do the same modifications made in this study need to be made in all subsequent settings to make the intervention externally valid? These questions can be difficult to answer with much certainty, and serve to highlight once again the importance of the iterative nature of the development and evaluation process [19].

When considering treatment fidelity in behavioural interventions, unplanned variation should ideally be limited [178]. In this study, the MBSR instructors were experienced

physicians and appropriately qualified mindfulness facilitators [217], but had never delivered the intervention to people exclusively with MS. Further, there was a high chance that many of the participants in the study would be quite disabled. Collecting qualitative data in these circumstances served to illuminate how such factors could impact on intervention delivery, and thus inform design and delivery of future courses in this context.

Another important consideration in optimisation work is optimising outcome measurement. For example, in feasibility testing it may become clear that there are too many measures, too few, that those chosen do not adequately capture the type of data which the research questions are seeking, or do not measure other important outcomes that only become apparent from qualitative participant feedback. Even with meticulous planning, this type of information may become apparent only through 'trial and error' [19].

3.3 Summary

This chapter has outlined the methods chosen for this thesis and the rationale for this choice. Methods are based on the suggestions of the MRC guidance [19] for developing and evaluating complex interventions to improve health. The next five chapters will describe the research process for each of these areas in detail, discuss the research findings, their implications, and suggest further steps for future research.

Chapter 4 Comorbidity in multiple sclerosis

4.1 Summary

This chapter describes the prevalence of comorbidity in people with MS from a nationally representative cross-sectional primary care database from Scotland. It starts by introducing what is known about comorbidity in MS, and describes key existing published studies on this topic. It then describes the methods used for the database analysis. Results are presented for people with MS versus age, sex, and deprivation matched controls. Following this, results are discussed in the context of the existing literature and knowledge gaps, before finishing with suggestions for future research.

4.2 Background

Research suggests that people with MS have reduced health-related QOL, and that in those with comorbidities this may be considerably worse [218, 219], with conditions such as fatigue, anxiety, and depression potentially synergistic in reducing QOL [9, 73]. Scores for QOL are lower in people with MS than in other LTCs, such as inflammatory bowel, musculoskeletal, and respiratory diseases [73, 220]. In people with MS, the impact of comorbidity on physical health-related QOL seems to impact more strongly on those who are more disabled. There appears to be a dose-response relationship, where greater number of comorbidities is associated with a progressive decline in QOL [220], although this has not been a uniform finding [180]. It has been suggested that some of the emerging MS pharmacological treatments may increase the risk of developing comorbidities, and that new therapies targeting improved QOL in people with MS should routinely take into account comorbidities as a matter-of-course, with a view to diminishing their deleterious impact [221].

Comorbidity is known to be associated with diminished functional ability in chronic diseases, being associated with a more rapid deterioration in Alzheimer's Disease [222], and with higher levels of mortality in many chronic conditions, including Parkinson's Disease [223]. In people with MS, comorbidity may adversely affect time to primary diagnosis, potentially by 'obscuring' the underlying pathology, where symptoms are attributed in error to another condition [224]. Such diagnostic delay is

particularly likely amongst male patients, smokers, those with comorbid mental health conditions, and in those with comorbid physical health conditions (vascular, auto-immune, musculoskeletal, gastrointestinal, visual, and obesity) [224]. The presence of comorbidity at the time of initial diagnosis is also associated with increased disability levels [224]. Comorbidity in MS is linked with increased hospital admissions [225], a higher number of CNS lesions on MRI measurement [226], and an increased mortality risk, particularly in those with comorbid depression [227].

4.2.1 Studies of comorbidity in MS

Marrie et al. [9, 228] reported findings from a national database in the USA, covering 8,983 individuals with MS, 34 conditions, and socio-demographic data. This included 30 physical comorbidities, and four mental comorbidities [9, 228]. Mental health problems were common in this study (48%, n=4,264) in all age groups and at all stages of disease progression. This ranged from 48.1% in those with a classification of 'mild' disability, to 56.4% in those with 'moderate' disability, and 46% in those with 'severe' disability levels [9]. Anxiety and depression were the most prevalent (19.5% and 43.9%, respectively, as compared to 16.6% and 16.2% in the US population in general). Women were 1.5 times more likely to be affected by depression than men, patients in their mid-forties were 1.5 times more likely to be diagnosed with depression than those over sixty, and those in the lowest income bracket were twice as likely to have depression than those in the highest. Overall, reporting a mental health comorbidity was more common amongst those of lower SES, in keeping with previous findings for the general population in the USA, although this trend did not reach statistical significance [9, 229].

The same study [228] found that physical comorbidities were more prevalent in male patients, African Americans, those of increasing age (over sixty years), and those of lower SES. Overall, 77.1% of respondents (of both genders) reported having one or more physical comorbidities, of which 25.6% had two, and 44.1% had three. The most frequent physical comorbidities were hypercholesterolaemia, hypertension, arthritis, irritable bowel, and lung disease. Half of the respondents were overweight, and of them, half were obese. Vascular comorbidities i.e. hypercholesterolaemia, hypertension, heart disease, diabetes, and peripheral vascular disease were common

(>50%). Almost 16% of all respondents had two or more vascular diagnoses, 4% had three, and 1% had four or more [228]. Such conditions have since been shown to increase disability progression greatly [230].

In Canada, Warren et al. [180] studied data from the Canadian Community Health Survey, reporting on 21 self-report comorbidities amongst a sample of 335 people with MS, described as nationally representative, though this seems unlikely on such a small sample. The mean number of comorbidities was 1.6, with up to 10% reporting in excess of eight other chronic conditions. This study reinforced the relationship between comorbidity and impaired health-related QOL, and also demonstrated that lower SES was an important compounding variable, with lower levels of education, and being in receipt of social support contributing significantly to reduced QOL.

In Taiwan, Kang et al. [231] described prevalence of comorbidity in MS from 30 conditions, derived from 989 patients who were compared against 4,490 non-MS controls. Data were taken from a national health insurance administrative research database. They described higher levels of various medical (autoimmune, endocrine, gastrointestinal, haematological, infectious, neurological, oncological, pulmonary, and renal) and psychiatric conditions (dementia, depression, psychoses) in people with MS.

Aside from the three studies listed above, the majority of studies of comorbidity in MS focus on small numbers of conditions, often with a particular disease focus (such as cardiovascular or autoimmune conditions), and originate mainly from Caucasian populations in Europe and in North America [232-236].

Scotland has the highest prevalence rates for MS worldwide [24], yet no previous studies exist focusing explicitly on the subject of comorbidity. In the UK, MS care is delivered via a MDT approach, although it remains a ‘specialist’ condition with a Consultant Neurologist usually taking the lead in patient care [44]. The primary role of the specialist is to manage the individual condition, but the GP also has a very important role, and holds a comprehensive electronic medical record. Data such as this can be used as a means of studying comorbidity in people with MS.

4.3 Methods

The aim of this study was to measure comorbidity in people with MS in Scotland by characterising the number and type of conditions compared with the general population.

The study used a dataset supplied by the Primary Care Clinical Informatics Unit, University of Aberdeen, UK. The dataset was created as part of national programme of research into multimorbidity, and anonymysed use has been approved by the UK NHS National Research Ethics Service [165]. The dataset contains information that was extracted in April 2007 on a total of 1,751,841 individual patients (around 1/3 of the Scottish population) from 314 general practices around Scotland. It is nationally representative in terms of age, sex, and deprivation [165]. All general practices in Scotland use electronic patient records, and have done so since the early 1990s. Electronic records are used for practice list management, recording of prescribing, recording of morbidities via a standard system of Read Codes by the Health and Social Care Information Centre (HSCIC - http://systems.hscic.gov.uk/data/uktc/readcodes/) and by the NHS Information Services Division (ISD) http://www.isdscotland.org/Health-Topics/General-Practice/GP-Consultations/Grouping-clinical-codes.asp).

The dataset holds information on 40 comorbidities, which were chosen for use based upon recent systematic review guidance on multimorbidity (n=11), conditions included in the UK GP Quality and Outcomes Framework (QOF) (n=16), and those specified as important for health services planning by NHS Scotland (n=26) [165]. In this dataset, MS has been defined as the presence of a Read Code ever being recorded for the condition. The code set was designed by the NHS ISD for Scotland. Of the remaining 39 morbidities, eight are mental health conditions and 31 are physical health conditions, and are based on Read Code recording by a clinician in the electronic patient record, or have been derived from prescribing data [165] – for more details regarding Read Code definitions see Appendix B.

For the purposes of this present study, the analysis was restricted to those aged over 25 years (n=1,268,859), as the number of individuals with a diagnosis of MS who are under 25 years of age was extremely low.

4.3.1 Statistical analysis

The main focus of the analysis was descriptive, comparing comorbidity in people with MS against those without. 'T' tests were employed as a means of examining differences between the mean numbers of morbidities, whilst Chi-squared tests examined for differences in percentages of individuals with comorbidities across variables [167].

Binary multivariate logistic regression was employed to examine for associations between comorbidities in those with MS versus those without, controlling for age, sex, and SES (measured by Carstairs score – [237]).

4.4 Results

Amongst the 1,268,859 individuals included in the analysis, 3,826 (0.3%; 95%CI 0.29-0.31) had a diagnosis of MS, and of these 2,767 (72.3%) were of female sex. Those with MS were slightly older on average, when compared to the general population (mean age 53.4 years, versus 51.2 years; $p<0.001$). Those with MS were slightly less deprived than the general population (mean -0.64 against -0.22; $p<0.001$) (Table 4.1).

Table 4.1 General sample characteristics, people with MS versus controls

	MS (>25yrs) n (%)	Non-MS (>25yrs) n (%)	Significance p
Total	3,826	1,268,859	
Gender (% female)	2,767 (72.3)	647,836 (51.1)	p<0.0001*
Mean age (SD)	53.4 (12.8)	51.2 (16.6)	p<0.0001*
Mean deprivation (SD)	-0.64 (3.0)	-0.2 (3.3)	p<0.0001*
Age group			
25-44	1018 (26.6)	507371 (40.0)	p<0.0001*
45-64	2083 (54.4)	471044 (37.1)	p<0.0001*
65-84	685 (17.9)	253915 (20.0)	p<0.001*
85+	40 (1.0)	36529 (2.9)	p<0.0001*
Deprivation Quintile			
Q1 least deprived	813 (21.2)	243545 (19.2)	p<0.001*
Q2	889 (23.2)	274878 (21.7)	p<0.01*
Q3	913 (23.9)	289037 (22.8)	p=0.06
Q4	687 (18.0)	241207 (19.0)	P<0.05*
Q5 most deprived	524 (13.7)	220192 (17.4)	p<0.0001*

* Statistically significant 'p' value

People with MS were significantly more likely to have more than one other chronic condition, following adjustment for age, sex, and deprivation (OR 2.44; 95% CI 2.26-2.64) (Table 4.2).

Table 4.2 Comorbidity prevalence and type in people with and without MS
*****Odds Ratios adjusted for Age, Sex and Deprivation Scores.

	MS n (%)	Non-MS n (%)	OR* (95% CI) Significance p
No comorbidity	1,027 (26.8)	597,363 (47.1)	0.20 (0.18-0.22) p<0.001*
One	2,799 (73.2)	671,496 (52.9)	2.44 (2.26-2.64) p<0.0001*
Two	714 (18.7)	159,293 (12.6)	1.49 (1.38-1.62) p<0.0001*
Three	546 (14.3)	97,368 (7.7)	1.86 (1.69-2.04) p<0.0001*
Four or more	669 (17.5)	136,847 (10.8)	1.61 (1.47-1.77) p<0.0001*
Any physical comorbidity	2,475 (64.7)	600,669 (47.3)	2.05 (1.90-2.21) p<0.0001*
Any mental health comorbidity	1,541 (40.3)	227,361 (17.9)	2.94 (2.75-3.14) p<0.0001*

* Statistically significant 'p' value

No differences were found between males and females with MS when considering age, deprivation, or total comorbidity count. However, mental comorbidity was significantly more likely amongst women with MS (OR 1.26; 95% CI 1.09-1.46) (Table 4.3).

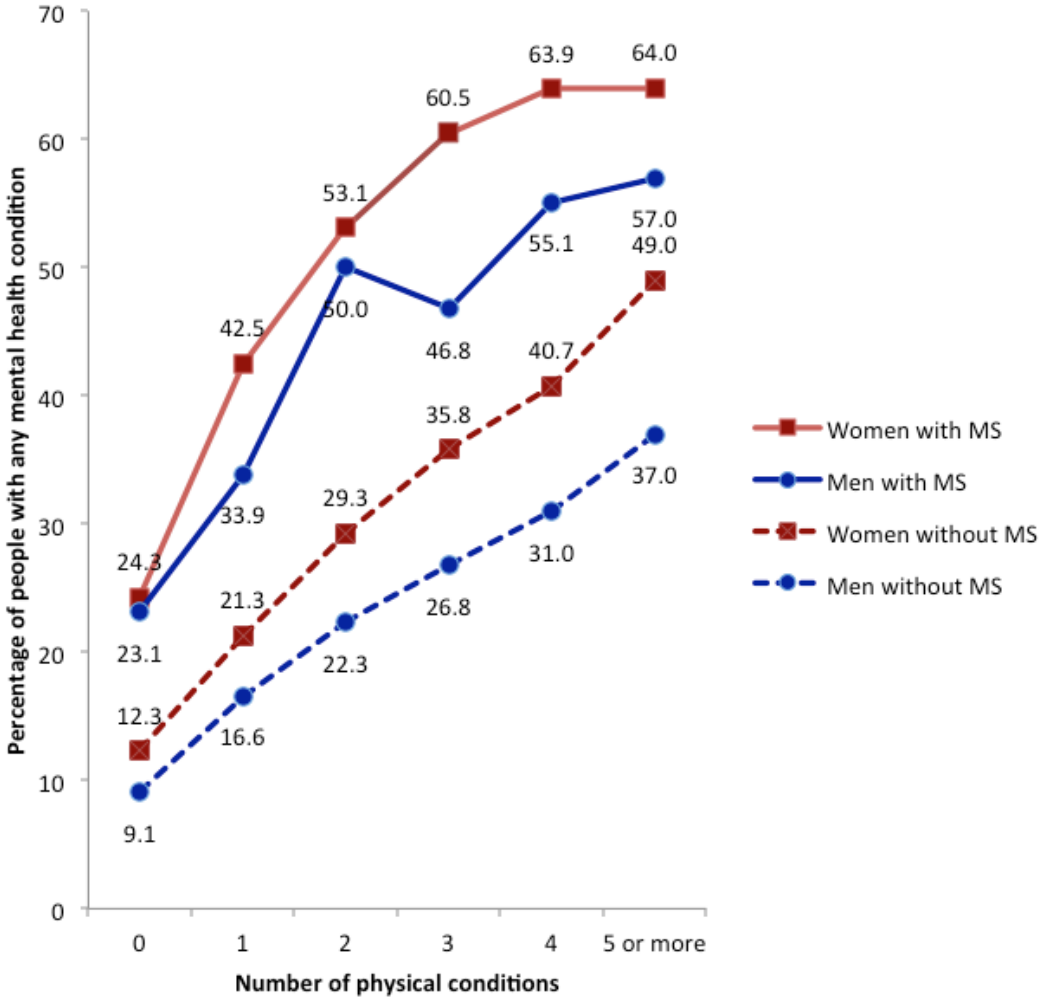
Table 4.3 Gender differences in co-morbidity in people with MS
*Odds ratios adjusted for Age and Deprivation scores

Physical Conditions (Including MS)	**MS Population Characteristics**		
	Female n (%)	**Male** n (%)	**OR* (95%CI) Significance p**
2+	1801(64.6)	678 (63.7)	1.07 (0.91 1.25) p=0.37
3+	1021 (36.6)	401 (37.7)	0.98 (0.84 1.14) p=0.55
Mental Conditions			
At least 1	1156 (41.8)	385 (36.4)	1.26 (1.09 1.46) p<0.05*
2+	112 (4.0)	55 (5.2)	1.02 (0.91 1.13) p=0.69

* Statistically significant 'p' value

Higher levels of chronic conditions were recorded for people with MS, after controlling for age, sex and deprivation (OR 2.44; 95%CI 2.26-2.64), and in particular for mental health comorbidity (OR 2.94; 95%CI 2.75-3.14). Those with MS were more likely to have one other (OR 2.44; 95%CI 2.26-2.64), two others (OR 1.49; 95%CI 1.38-1.62), three others (OR 1.86; 95% CI 1.69-2.04), or four or more other non-MS conditions than those unaffected by MS (OR 1.61; 95%CI 1.47-1.77) (Table 4.2). As the number of physical morbidities rose, both males and females with MS had consistently higher levels of mental health comorbidity than the general population (Figure 4.1)

Figure 4.1 Association between number of physical conditions and presence of any mental health condition

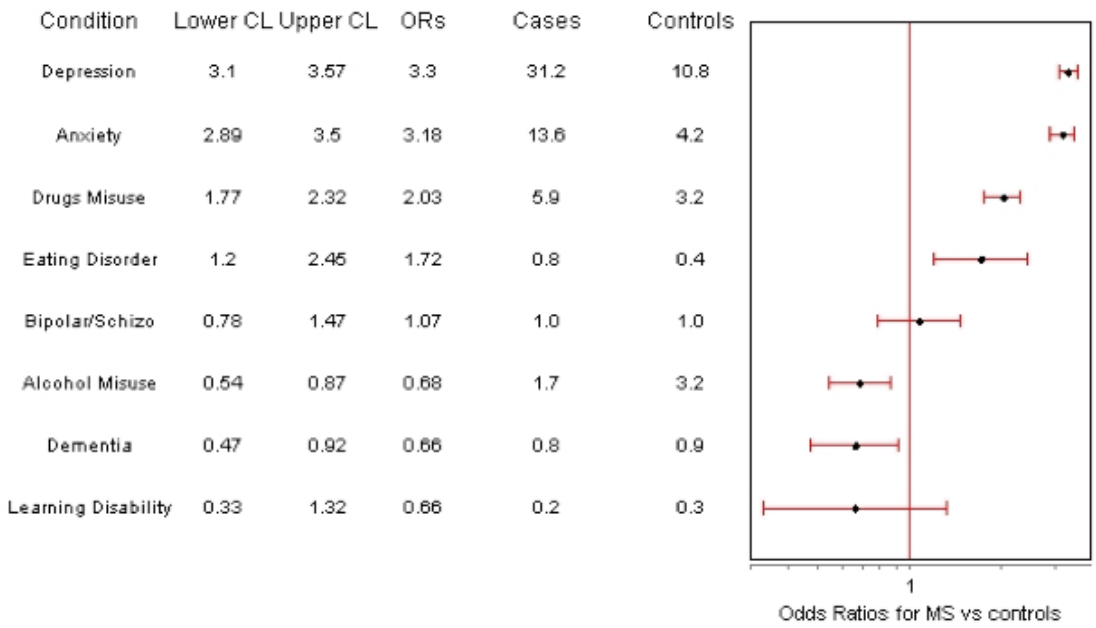


4.4.1 Mental health comorbidity in people with MS

After adjustment for age, sex, and deprivation, prevalence was higher for four of the eight mental conditions examined for amongst those with MS (Figure 4.2); the highest being depression (OR 3.33; 95%CI 3.10-3.57), then anxiety (OR 3.18; 95%CI 2.89-3.50), and then drug misuse (OR 2.03; 95%CI 1.77-2.32). Prevalence was also higher for a diagnosis of an eating disorder (OR 1.72; 95%CI 1.20-2.45), but the numbers included in this group were small (n=31). Schizophrenia/bipolar (OR 1.07; 95%CI 0.78-1.47) and learning disability (OR 0.66; 95%CI 0.33-1.32) were not significantly different between those with MS and controls, but dementia (OR 0.66; 95%CI 0.47-

0.94) and alcohol misuse (OR 0.68; 95%CI 0.54-0.87) were both significantly less common in those with MS as compared to the general population.

Figure 4.2 Odds ratios for individual mental health conditions: people with MS versus controls

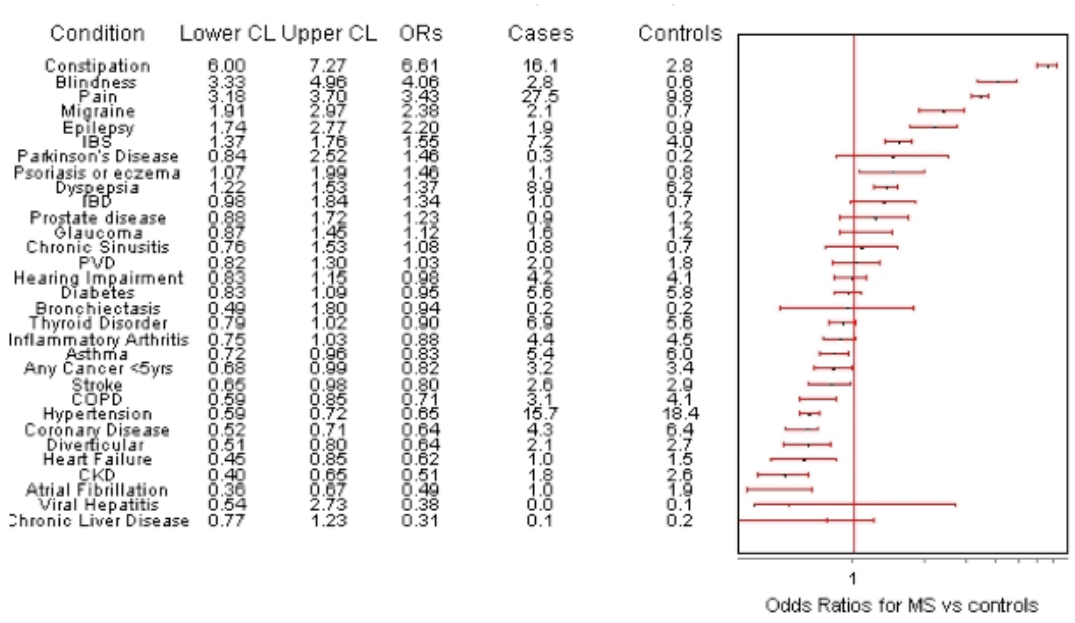


Note on abbreviations [12]: Depression = *Read code recorded in last 12 months OR ≥4 anti-depressant prescriptions (excluding low dose tricyclics) in last 12 months*; Anxiety = *Anxiety & other neurotic, stress related & somatoform disorders, Read code in last 12 months OR ≥ 4 anxiolytic/hypnotic prescriptions in last 12 months OR ≥4 10/25mg amitriptyline in last 12 months & do not meet the criteria for .'Pain.'*; Drugs Misuse = *Other psychoactive substance misuse*; Eating Disorder = *Anorexia or Bulimia*; Bipolar/*Schizo = Schizophrenia (and related non-organic psychosis) or bipolar disorder, Read code ever recorded/recorded in last 12 months (code dependent) OR Lithium prescribed in last 168 days.*

4.4.2 Physical health comorbidity in people with MS

Of the thirty other physical conditions included in the analysis, the prevalence was higher amongst those with MS for 10 conditions, no different for nine, but lower for 11 (Figure 4.3).

Figure 4.3 Odds ratios for individual physical health conditions: people with MS versus controls



Note on abbreviations [12]: Constipation = *≥4 laxative prescriptions in last year*; Pain = *≥4 prescription only medicine analgesic prescriptions in last 12 months OR ≥4 specified anti-epileptics in the absence of an epilepsy Read code in last 12 months;* Migraine = *≥4 prescription only medicine anti-migraine prescriptions in last year*; Epilepsy = *Read code ever recorded AND antiepileptic prescription in last 12 months*; IBS = *Read code ever recorded OR ≥ 4 prescription only medicine antispasmodic prescription in last 12 months*; Parkinson's Disease= *Parkinson's Disease and Parkinsonism;* Psoriasis or Eczema = *Read code ever recorded AND ≥ 4 related prescriptions in last 12 months (excluding simple emollients)* Dyspepsia = *≥ 4 prescriptions in last 12 months excluding antacids AND NOT (≥4 NSAIDS OR ≥4 aspirin/clopidogrel)* IBD = inflammatory bowel disease; PVD = *Peripheral vascular disease*; Stroke = *Stroke and Transient ischaemic attack*; COPD = *Chronic obstructive pulmonary disease*; CKD = *Chronic kidney disease*; Inflammatory Arthritis = *Rheumatoid arthritis, other inflammatory polyarthropathies & systematic connective tissue disorders*; Asthma = *Read code ever recorded AND any prescription in last 12 months*

The highest prevalence was recorded in those with MS (versus controls) for constipation (OR 6.61; 95%CI 6.00-7.27), followed by visual impairment (OR 4.06; 95%CI 3.33-4.96), chronic pain (OR 3.43; 95%CI 3.18-3.70), migraine (OR 2.38; 95%CI 1.91-2.97), and then epilepsy (OR 2.20; 95%CI 1.74-2.77). On the other hand, prevalence was significantly lower amongst those with MS for most of the cardiovascular conditions, including atrial fibrillation (OR 0.49; 95%CI 0.36-0.67), chronic kidney disease (OR 0.51; 95%CI 0.40-0.65), heart failure (OR 0.62; 95%CI

0.45-0.85), coronary heart disease (OR 0.64; 95%CI 0.52-0.71), and hypertension (OR 0.65; 95%CI 0.59-0.72).

4.5 Discussion

4.5.1 Key findings

The present study examined physical and mental health comorbidity in people with MS in a large primary care clinical dataset, and has shown that having additional LTCs is commonplace amongst this group. Mental health comorbidity was particularly common and this association increased in a linear fashion as the number of physical comorbidities increased. Females were statistically significantly more likely to have mental health comorbidity that men with MS. Cardiovascular comorbidities were notably low in prevalence.

4.5.2 Comparison with literature

This present study demonstrated that mental health comorbidities (anxiety and depression in particular) were almost three times more common in those with MS, as compared to the general population. These levels are comparable to those reported by other researchers in the USA and Ireland [9, 238], and to findings from a recent systematic review examining global prevalence rates [51]. This current study found a higher prevalence of mental health comorbidities in women with MS. Recently, another UK-based study, which examined a cross-sectional web-based self-report database (n with MS = 7,786) [239], reported significantly higher anxiety scores on the Hospital Anxiety and Depression Scale (HADS) for women with RRMS versus men with the same phenotype. Similarly, a recent retrospective database analysis of North American patients with MS (n with MS = 711) found that anxiety was more prevalent in female patients, but depression was not significantly different between the sexes [240]. However, an older population-based survey from Canada (n with MS = 322) suggested a higher prevalence of depression in females [241], whilst a Portuguese cross-sectional study (n with MS = 325) found that female MS patients scored higher than male patients on both anxiety and depression scales on the HADS [242]. Other studies have not found any significant differences in mental health

comorbidities between the sexes in MS patients [243, 244]. In the general Scottish population, however, mixed physical-mental comorbidity is known to be more prevalent in women [245].

Both anxiety and depression are associated with greater levels of suicidality in those with MS, whilst depression is linked to reduced health-related QOL and is in itself a noted predictor of increased morbidity and mortality [5, 57]. Amongst those with MS, anxiety is known to increase following initial diagnosis. It may be particularly problematic and is more prevalent in females [57, 240]. Anxiety can predispose to increased social difficulties, higher levels of somatic complaints [246], and higher usage of alcohol [57]. Depression is poorly understood in MS. The suggestion has been made that depression could relate to the underlying neuro-inflammatory process [247, 248]. This could fit with the proposed auto-immune aetiology in MS [248], but it is important to note that depression is a common finding in many physical diseases [249], and it remains likely that multiple factors contribute to depression in those with MS.

The prevalence of bipolar disorder (BPD) was not significantly different between those with MS and controls in this study. Recent research suggests an increased prevalence of the condition amongst those with MS [250]. A growing literature around the world suggests that BPD may in fact be frequently misdiagnosed in the primary care setting as major depressive disorder (MDD) [251, 252], which has implications for treatment, as antidepressants, which are a key treatment in MDD, can actually make BPD worse, and untreated BPD is associated with high rates of suicide [250].

Comorbidity of physical health conditions was present in almost two thirds of those with MS in this study, being twice as likely when compared to the general population (after controlling for age, sex, and deprivation). Nervous system comorbidities were notably prevalent, with chronic pain, migraine, and epilepsy all being over two times as likely amongst those with MS. These findings are in accord with those in the existing literature, with Koch et al. [253] reporting seizures being present in up to 8.3% of those with MS, and Marrie et al. [254] reporting global prevalence estimates for epilepsy in MS at 3.1% (versus 1.9% in the present study). Kratz et al. [255]

reported rates for chronic pain of up to 50% in people with MS. Chronic pain can directly impact levels of psychological morbidity, diminish health-related QOL, increase disability, and drive up health service utilisation [255]. Migraine has also been reported as more prevalent amongst those with MS [256], although it is important to note that there may be some overlap in terms of pathology between the conditions, with cortical spreading depression (a putative pathological mechanism underlying migraine –[257]) thought to be enhanced by cortical demyelination [256]. Visual impairment was more than four times as likely in those with MS in this present study, in keeping with similar studies in this area [258]. This probably represents optic neuritis, a common problem amongst those with MS, and a condition with implications for lasting visual function and health-related QOL [258]. Indeed, qualitative studies have found that from the range of possible disabilities ensuing as MS progresses, patients tend to report that loss of visual function and diminished ambulatory ability matter most [21].

This present study also found that certain gastrointestinal conditions (constipation, dyspepsia, irritable bowel syndrome - IBS) stand out as more common amongst those with MS. Similarly high levels of IBS were reported in a recent systematic review by Marrie et al. [259]. It is possible that these findings may relate to neurogenic bowel dysfunction, known to be common in people with MS [260], raising the question whether such comorbidities are distinct disease entities, or whether they in fact relate directly to MS disease activity.

An unexpected finding in this current study was that of lower recorded cardiovascular conditions amongst the MS population, when compared to controls, particularly surprising given that the sample is nationally representative for the Scottish population. As previously noted, cardiovascular pathologies represent a potentially important group of comorbidities in people with MS. Cardiovascular disease can increase disability and mortality in this group [227, 230] and, as in non-MS patients, may have detrimental effects on brain mass and function [261, 262]. Recent systematic review evidence suggests that those with MS are more likely to be diagnosed with cardiovascular comorbidities [263]. The exact reasons remain unclear at present, and the review authors point out that traditional cardiovascular risk factors (diabetes, dyslipidaemia, hypertension, obesity) are not so easily identifiable as

causative amongst those with MS. Inflammation may play a pathological role in both MS and these cardiovascular conditions [263], but the immune profile in MS is very complex, limiting comparisons [38, 94].

As noted above, certain physical conditions were found to be particularly prevalent in the present study, and whether this relates to the direct consequences of MS disease activity, its treatment, or other mechanisms remains unclear. It is possible that common pathologies may co-exist in MS and other chronic conditions, such as chronic inflammation [264]. The low level of cardiovascular conditions is also notable, but resonates with findings from Smith et al. [265], who used the same database, and reported similar findings amongst those affected with schizophrenia and BPD. This might suggest that there is under-diagnosis of cardiovascular comorbidities in the primary care setting in such chronic conditions. With respect to MS, it is not clear why this is the case. It seems unlikely to result from less contact with primary care [87, 266]. Another explanation may relate to the diagnostic and prognostic difficulty associated with the condition, where the significance of new symptoms can be challenging for clinicians [87]. MS patients may be at various stages of disease progression, and early in the condition there may be little perceived need for contact with primary care, or a neurologist [87]. Very little is known about whether cardiovascular comorbidities might present differently in people with MS, but in general, comorbidity in this population is associated with diagnostic delay, and reduced treatment adherence [267]. As intervention is likely to be beneficial, it seems important that clinicians adopt a vigilant approach to cardiovascular risk factors when caring for patients with MS.

4.5.3 Strengths and limitations

A strength of the current study is the large, nationally representative dataset used, from the country with the highest prevalence of MS worldwide. It included a wide range of conditions, including both mental and physical, with data on age, gender, and deprivation (as estimated from postcode).

Weaknesses included the fact that the dataset was not designed specifically for MS research. It did not have information on disease duration and also did not specify

whether comorbidities pre-dated the diagnosis of MS, or whether comorbidity diagnoses increased/decreased after MS diagnosis. The cross-sectional nature of the dataset meant that associations could be drawn, but causal inferences could not. Further work using prospective cohort data would be important in trying to seek temporal relationships. As per other routine data analyses, the dataset is dependent on the recording quality by front-line clinicians, which may vary. Data recording in General Practice in the UK is thought to be good, but as Khan et al. [268] note in a recent systematic review, the positive predictive value (PPV) for a MS Read Code is limited to around 0.60, meaning that there is a distinct possibility that some of the people included in this analysis may not actually have MS. A further limitation is that recorded rates for anxiety and depression in the database used in this study may be an underestimate of true prevalence, given that only around a third of community populations seek help for these conditions in primary care [269] and a recent trend has been noted for UK GPs increasingly to record symptom codes rather than diagnostic codes [270, 271]. In this study, coding for anxiety and depression were based on Read Code recording plus prescribing data (Appendix B). Reasons for not recording diagnostic codes in primary care are known to include spontaneous symptom resolution, patients presenting with primarily physical symptoms, and stigma [272]. John et al. [273] recently assessed sensitivity, specificity and PPV for common mental disorders in the General Practice Research Database (GPRD) using various algorithms and the Mental Health Inventory-5 (MHI-5) as a 'gold-standard' diagnostic tool. They found that a Read Code indicating a historical diagnosis of depression or anxiety (over a ten year period) plus a current diagnosis (treated or untreated) had a specificity of 0.96, a sensitivity of 0.29, and a PPV of 0.76, and that adding in current symptoms codes rendered little change to specificity (0.95) and PPV (0.74), but facilitated a slight increase in sensitivity to 0.32. Nine percent of false negatives had current symptom codes, and in general were more likely to have chronic pain (71%) or other chronic comorbid conditions (50%). Read codes are generally more accurate in chronic conditions, and largely considered as being well recorded in practice, but in some cases may reflect 'activity' with a patient, rather than application of a diagnosis per se [268]. The fact that prescribing data was used for the generation of certain comorbidities is also a limitation, in that some drugs have unlicensed, or non-standard uses that may well feature amongst those with MS – for

example the use of analgesics or anti-convulsant medication for spasticity management, and this may have led to some misclassification.

The comorbidities included in the database come from General Practice and prescribing data, and in the specific case of MS, some of these may actually represent so-called ‘concordant conditions’ i.e. may represent aspects of the same pathological risk profile, and possibly the same disease management schedule [274]. This concept is not well described in the research literature for MS, and may form an important avenue for future enquiry. For example, differentiating whether a condition is an entity distinct from MS, or is a complication of MS can influence treatment decisions. If a comorbid condition unrelated to MS pathology leads to worse outcomes, then treatment may focus on the comorbidity, but if the condition is a result of MS disease activity, then focusing treatment on the underlying disorder (MS), as well as the condition makes sense.

4.5.4 Implications for practice/policy/future research

Clinicians and researchers alike should be aware that comorbidity is common in people with MS. This is particularly true for mental health comorbidity, where an association increases in line with the number of physical conditions present. Treating MS in isolation may fail to address this burden, which can be a stressful experience for people with the condition. Future research could focus on the development of integrative treatment strategies that acknowledge this difficulty and contribute to enhanced stress- and self-management skills.

4.6 Conclusions

This current study has confirmed that people with MS in Scotland commonly experience comorbidity, at much higher levels than amongst those in the general population. Certain conditions were found to be much more likely to be present in those with MS. Among mental health conditions, anxiety and depression were particularly common. Amongst physical conditions, nervous system and gastrointestinal comorbidities predominated. Cardiovascular conditions were less common in those with MS, but this could be due to decreased case finding in those

with MS and further research in this area is required. As per the general population, increasing numbers of physical conditions was associated with higher levels of mental health comorbidity, and this was more marked in those with MS. The consequences of mental health comorbidity in MS are largely unknown. This too deserves further scrutiny. Effective mental health treatments in MS seem necessary, and may require to be tailored to meet the specific needs of this group [275, 276].

Chapter 5 A systematic review of mindfulness based interventions for people with multiple sclerosis

5.1 Summary

This chapter describes the findings from a systematic review of the evidence for effectiveness of MBIs in people with MS. A brief background summary focuses the reader on why this review was necessary, and then the methods used to perform the review are described. Following this, the results section presents data synthesised from randomised and controlled studies on the use of MBIs in people with MS. The main findings are then summarised, compared with the relevant literature, including those developments taking place since the review was completed. Finally, implications and suggestions for future research and practice are suggested.

5.2 Background

Self-management forms an important component of living with a diagnosis of MS, which can mean developing resilience towards distressing events, or adopting a flexible approach towards both symptoms and the trials and tribulations of daily life [277, 278]. Such adaptive changes may not come naturally to an individual, and as such a form of psycho-education may be required [3]. Traditional approaches in this regard often involve some form of CBT [11], or a more general composite of 'advice' from experienced clinicians, fellow patients, or support groups [44]. However, a standardised form of stress management designed to build distress tolerance and psychological flexibility is not routinely available to people with MS in the UK NHS.

Mindfulness training for people with MS has been suggested as a means to '*..enhance general features of coping with distress and disability in everyday life, as well as under more extraordinary conditions of serious disorder or stress.*' [279]. In certain adult populations living with LTCs, and also amongst healthy individuals, MBIs have shown promise for improving cognitive abilities, such as selective and executive attention, unfocussed sustained attention, memory and other executive functions [15, 280]. As a health care intervention, mindfulness has been studied in a variety of

settings and in several different medical conditions [14, 16, 17, 154]. These studies have generally reported beneficial effects in relation to both physical and psychological symptoms (including stress), although quality issues are commonplace. Most studies have not been well designed, did not compare a MBI against an active control group, and did not report findings in line with suggested CONSORT criteria [159]. Where MBIs have been compared against active controls, findings suggest that MBIs are effective, but with effects comparable to other active interventions (such as CBT or antidepressants) [159]. A widespread consensus on the applicability and utility of MBIs in managing stress associated with LTCs has not been established.

Systematic reviews and meta-analyses have shown MBIs to be efficacious in treating anxiety and recurrent depression [18, 281]; in people who have had a stroke – improving anxiety, depression, fatigue, and QOL [282]; and in somatisation disorders (such as fibromyalgia, CFS, IBS) for improving subjective fatigue, anxiety, depression, QOL and physical functioning [283]. MBIs have weaker benefits in people with chronic pain [159, 284] and in people who are 'stressed' [159]. Despite many of these LTCs being relevant and/or sharing common features with symptoms experienced by people with MS, the use of MBIs in the MS population has not been widely studied.

5.2.1 Why undertake a systematic review on mindfulness-based interventions in people with MS?

As described in Chapter 2, MS is thought to be a very stressful condition. As described in Chapter 4, MS is associated with high levels of comorbidity, which is believed to be stressful [49], and high levels of stress in the context of multimorbidity is associated with excess mortality [50]. People with MS value learning effective stress management techniques, but report that they are not always available [62]. Amongst psychological interventions for people with MS, CBT has the most evidence for effectiveness [10, 11, 120], but questions remain regarding lasting efficacy. This may be related to mechanisms of action [285], where CBT is thought to operate via predominantly 'top-down' mechanisms, with cognitive restructuring exerting an increase in inhibitory executive control over lower axis brain structures [286]. MBIs are proposed to work differently, with both 'top-down' cognitive and 'bottom-up'

somatic mechanisms suggested, alongside the added component of 'meta-awareness' [132], which may make them more effective than established CBT therapies (see Chapter 2 for more details regarding proposed mechanisms of action for MBIs).

At the time of conducting this review, there were no published systematic reviews on the use of MBIs for people with MS. The aim of this study was to delineate the existing evidence for effectiveness of MBIs in people with MS by carrying out a systematic review. The specific research questions addressed in the review were:

1) What effects, if any, do MBIs have on perceived stress in people with MS?
2) What effects, if any, do MBIs have on mental and physical health in people with MS?
3) What effects, if any, do MBIs have on QOL in people with MS?
4) What evidence, if any, is there that MBIs are cost-effective in people with MS?
5) What gaps are there in the literature concerning the effectiveness of MBIs in people with MS, across variables such as differing age, gender, ethnicity, SES, level and type of comorbidity?

5.3 Methods

5.3.1 Search strategy

In May of 2013 a systematic search of both the published and unpublished empirical literature was undertaken via six key electronic bibliographic databases, including Allied and Complementary Medicine Database (AMED), CINAHL, Cochrane Register of Controlled Trials, EMBASE, MEDLINE, and PSYCHinfo. ProQuest Dissertation and Thesis Database was also searched and MS/mindfulness researchers were contacted, in order to identify any additional published/unpublished trials. Medical subject headings were selected and combined with key words pertaining to MS and mindfulness (Figure 5.1) to create a search strategy to be finalised for use in MEDLINE (being amended as required for use in the other databases). The search strategy employed appropriate controlled vocabulary, search symbols and Boolean operators. Dates searched (1980-2013), Language of reporting (English), and

Research Subjects (Human) served as delimiters. The search also extended to the Grey Literature, accessing the Science Citation Index, reference lists and citation searching from relevant published trials and reviews, and included making contact with experts in the field. All results were stored and managed via Endnote.

Figure 5.1 Search history: OVIDsp - MEDLINE with Full Text 3/5/13

S1. exp multiple sclerosis/ or exp multiple sclerosis, chronic progressive/ or exp multiple sclerosis, relapsing-remitting/ or exp neuromyelitis optica/

S2. limit S1 to (english language and humans and yr="1980-current"

S3. ("disseminated sclerosis" or "demyelinating disease" or devic or "acute disseminated encephalomyelitis" or "multiple sclerosis" or "neuromyelitis optica" or "optic neuritis" or "transverse myelitis").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

S4. limit S3 to (english language and humans and yr="1980 -Current")

S5. exp Meditation/

S6. limit S5 to (english language and humans and yr="1980 -Current")

S7. ("breathing exercise$" or "breathing technique$" or mindful$ or meditat$ or relaxation or vipassana or yog$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

S8. limit S7 to (english language and humans and yr="1980 -Current")

S9. S2 or S4

S10. S6 or S8

S11. S9 and S10

Articles: 278

5.3.2 Selection criteria

Studies for inclusion were selected on the basis of the SPIO model (Study design, Participants, Interventions, and Outcomes), which is adapted from the PICOs model (Population, Interventions, Comparison, Outcomes) [287] (Table 5.1).

Table 5.1 SPIO narrow screen inclusion/exclusion criteria

	Inclusion criteria	**Exclusion criteria**
Study design	Randomised controlled trial Controlled trial	Qualitative studies Single case study Systematic reviews Literature reviews Guidelines Audit
Population	Age >18 years Any diagnosis of MS	<18years old Diseases other than (and not including) MS
Intervention	Any MBI	Psychotherapy Drug treatments Manual therapy (i.e. massage)
Outcomes	Perceived stress Anxiety Depression Health-related QOL Pain Personal wellbeing Social participation	

Studies included RCTs and controlled trials (CTs) only. A definite MS diagnosis in an adult patient (>18years of age) was set as acceptable for inclusion in the review. As MBIs can vary in content, core ingredients including body awareness, breath awareness, and mindful movement (as per the standard MBSR components) were identified as pre-requisite for inclusion. MBSR was selected as it was the first MBI to be introduced as a health care intervention, inaugurated in the nineteen-eighties in North America [151]. The primary outcome measure for the purposes of this study was perceived stress. Other secondary outcomes were mental health measures, physical health measures, psychosocial measures, and health care utilisation.

Bibliographic records identified through the searches were assessed for relevance via broad inclusion criteria (i.e. 'multiple sclerosis' and 'mindfulness') and all papers deemed relevant were then subject to screening via the SPIO model to determine eligibility. Those selected papers were then methodologically appraised. The low number of studies yielded from the search led to a decision not to exclude any papers on the sole basis of poor methodological quality. The methodological issues identified are discussed in the text below.

5.3.3 Quality appraisal

The risk of bias was determined via the assessment tool suggested by the Cochrane Collaboration [288], summarising the potential risk of bias for major outcomes. Each outcome was graded individually as high, unclear, or low risk. Data was sought to determine whether adequate evidence was present for sequence generation, concealment of allocation, participant, personnel and outcome-assessor blinding, completeness of outcome data, selective reporting of outcomes, or any other sources of bias.

5.3.4 Data extraction

In conjunction with supervisors and other colleagues involved in the review (Dr Maggie Lawrence - ML; Dr Joanne Booth - JB), a data extraction tool was developed, which was adapted from one used in a recent systematic review examining the role of MBIs amongst those having suffered a transient ischaemic attack or stroke [282] (Appendix C). Data extraction included information on the study methodology and design, the population being reviewed, the interventions employed, and the study outcomes. Two independent reviewers screened the studies and extracted data separately. The broad screen was carried out by the researcher (RS) and a research assistant – Miss Sharon Byrne (SB), whilst RS and JB subsequently completed the narrow screen. Any discrepancy was subject to a third party opinion by a senior reviewer i.e. the researcher's supervisor (Professor Stewart Mercer - SM).

5.3.5 Data synthesis

The heterogeneous nature of the results from the search and review rendered meta-analysis impossible, and findings are thus presented in a narrative format.

5.4 Results

Searching of the databases identified a total of 1,049 studies. After broad and narrow screens (Figure 5.2), only three papers were judged appropriate for inclusion. These were Mills and Allen [289], Grossman et al. [177], and Tavee et al. [290] (Table 5.2). Excluded papers at the narrow screen stage are detailed in Table 5.3. Several attempts (three) were made to contact Authors Mills and Allen [289] and Tavee et al. [290] for further information via listed email addresses, but no replies were ever received.

Figure 5.2 Search results flow diagram

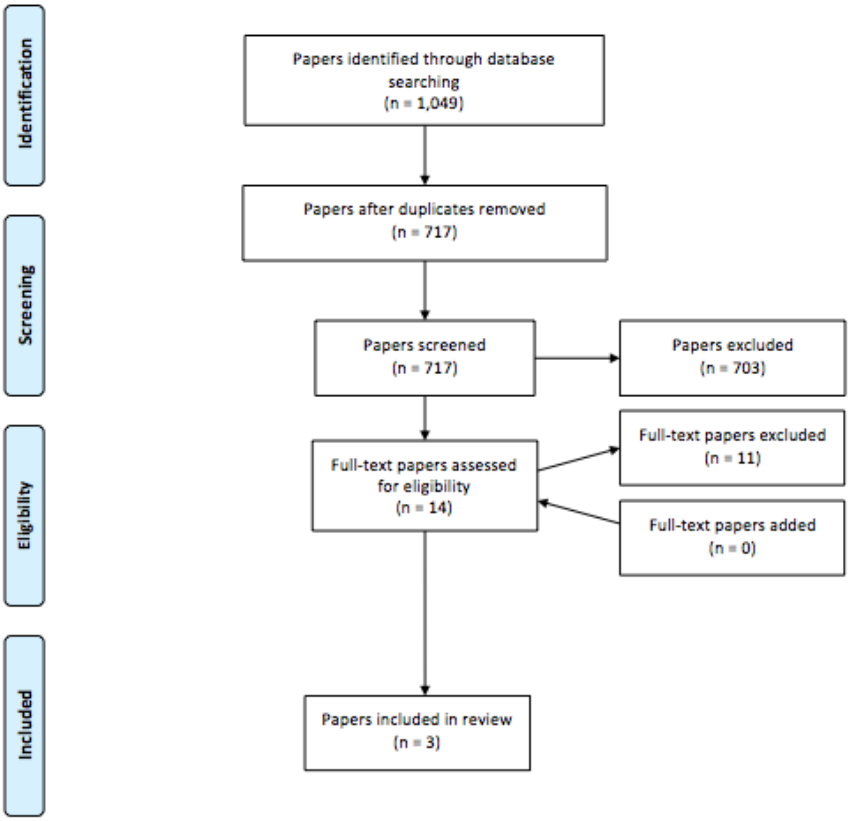


Table 5.2 Study characteristics

Study (**Country**)	**Study design** (**Setting**)	**Sample size** (**Attrition**%)	**Type of intervention** (**duration**)	**Outcome measures**	**Data collection**
Mills and Allen [289] (**Wales**)	RCT (Patients home)	n = 16 (12.5%)	Mindful breathing Mindful movement (Tai Chi) Self compassion Home study material (6/52 duration)	POMS Standing balance Symptom rating questionnaire	Baseline Post intervention 3 months post intervention
Grossman et al. [177] (**Switzerland**)	RCT (University hospital)	n = 150 (5%)	Mindful breathing Mindful movement (Yoga) Body scan Home study material (8/52 duration)	CES-D STAI MFIS HAQUAMS PQOLC Neuropsych	Baseline Post intervention 6 months post intervention
Tavee et al. [290] (**United States**)	CT (University hospital)	n = 17 (43%)	Mindful breathing (Samatha) Mindful movement (Tai Chi) Walking meditation (8/52 duration)	SF-36 MFIS VAS Physical role Vitality PDDS	Baseline Post intervention NR

1.RCT - Randomised controlled trial; 2.CT - Controlled trial; 3.CES-D Center for Epidemiological Studies Depression scale; 4.HAQUAMS - Hamburg Quality of Life Questionnaire in Multiple Sclerosis (German); 5.MFIS - Modified Fatigue Impact Scale; 6.POMS - Profile of Mood States; 7.PQOLC - Profile of health related Quality Of Life in Chronic disorders (German); 8.SF-36 - Short Form-36; 9.STAI - Spielberger Trait Anxiety Inventory; 10.VAS - Visual Analogue Scale for bodily pain; 11.PDDS - Patient Determined Disease Steps; 12. Neuropsych. – Neuropsychological assessment; 13. NR - Not recorded.

Table 5.3 Excluded studies

Author (Study title)	Factors necessitating exclusion
Ahmadi et al. [291] The Effects of a Yoga Intervention on Balance, Speed and Endurance of Walking, Fatigue and Quality of Life in People with Multiple Sclerosis	Yoga intervention. No emphasis on mindfulness described.
Doulatabad et al. [292] The effects of pranayama, hatha and raja yoga on physical pain and the quality of life of women with multiple sclerosis	Yoga intervention. No full text available.
Garrett et al. [293] Exercise in the community for people with multiple sclerosis—a follow-up of people with minimal gait impairment	Yoga intervention. No emphasis on mindfulness described.
Garrett et al. [294] Exercise in the community for people with minimal gait impairment due to MS: an assessor-blind randomized controlled trial	As Garrett et al. study above – elaboration on prior findings.
Granmayeh et al. [295] The effects of Mindfulness-Based Stress Reduction programme on physical symptoms, quality of life, and mental health in patients with multiple sclerosis	Full paper unavailable in English.
Hankin [296] Mindfulness-Based Stress Reduction in couples facing multiple sclerosis: Impact on self reported anxiety and uncertainty	Uncontrolled trial.
Jajvandian et al. [297] Influence of 6-week yoga on depression and fatigue in patients with multiple sclerosis, North Khorasan, northeastern Iran	Full paper unavailable in English.
Nordin et al. [298] Cognitive behavioural therapy in multiple sclerosis: a randomized controlled pilot study of acceptance and commitment therapy	Acceptance and Commitment Therapy intervention.
Oken et al. [299] Randomized controlled trial of yoga and exercise in multiple sclerosis	Yoga intervention. No emphasis on mindfulness described.
Pritchard et al. [127] Impact of Integrative Restoration (iRest) Meditation on Perceived Stress Levels in Multiple Sclerosis and Cancer Outpatients	Yoga intervention. No emphasis on mindfulness described.
Velikonja et al. [300] Influence of sports climbing and yoga on spasticity, cognitive function, mood and fatigue in patients with multiple sclerosis	Yoga intervention. No emphasis on mindfulness described.

5.4.1 Study characteristics

The studies included were derived from Wales [289], Switzerland [177], and the United States [290]. Mills and Allen [289] and Grossman et al. [177] undertook RCTs, whereas Tavee et al. [290] opted for a non-randomised CT. None of the studies employed an active control for comparison with the MBI. In the Grossman et al. [177] trial, participants were recruited from outpatient Neurology clinics, and the trial was carried out in a university hospital location, as was the case in the Tavee et al. [290] study. In the Mills and Allen [289] trial, recruitment was from either the participants General Practitioner or by a Physiotherapist.

There were 183 participants in total across the three studies. Attrition rates varied, with Grossman et al. [177] reporting very low rates (5%), and notably high overall attendance (92%). Mills and Allen [289] described attrition rates of 12.5%, noting that bereavement, and dislike of the Tai Chi-based mindful movement component, accounted for their dropouts. The highest attrition rates (43%) were described by Tavee et al. [290], who described transportation issues, or lack of enthusiasm for the intervention as reasons accounting for this finding.

A complicating factor in the Tavee et al. [290] study was that the authors presented findings for a heterogeneous participant group, in that the results for people with MS were in some cases mixed together with individuals with peripheral neuropathy. This limited interpretation of some of their findings.

Data collection was most comprehensive in the Grossman et al. [177] study (baseline, post-intervention, and six-month follow up), although Mills and Allen [289] also collected at three time points (baseline, post-intervention, and three-month follow up). Tavee et al. [290] collected data at baseline and at the completion of the intervention only (Table 5.2).

5.4.2 Intervention characteristics

The Grossman et al. [177] study intervention closely resembled MBSR. The Mills and Allen [289] and the Tavee et al. [290] studies employed non-standard components, with Tai Chi and Qi Gong exercises. Nevertheless, all of the three studies had broadly

comparable ingredients, with emphasis on mindful-movement, mindful-body awareness, and mindful-breath awareness. Grossman et al. [177] and Tavee et al. [290] both undertook group interventions, whilst Mills and Allen [289] delivered an intervention on a one-to-one basis.

In the Grossman et al. [177] study, experienced and certified trainers delivered the eight week, 2.5 hour session intervention weekly, and included a seven-hour session at the sixth week. Mindfulness practices were emphasised sitting, lying, and in the yoga asana postures. Home practice of up to 40 minutes per day was also encouraged, and was recorded (with Grossman et al. [177] also being the only researchers to record home practice times). Tavee et al. [290] started their intervention with a four hour introductory session, which was followed by eight weekly 1.5 hour sessions, all being facilitated/taught by a Buddhist Monk. Sessions in the Tavee et al. [290] study included a Samatha meditation (a sitting practice where the goal was simply to observe the breath), and mindful-movement (Tai Chi/Qi Qong/walking meditation). Home practice was encouraged, but not recorded. Alternatively, Mills and Allen [289] opted for six sessions, which were individualised to the participants, but included mindful-movement (Tai Chi/Qi Gong), breath and posture awareness, and the cultivation of self-compassion. Mills and Allen [289] included self-study material, but further details on its uptake/usage were absent. Details pertaining to their course facilitators were not specified (Table 5.2).

5.4.3 Participant characteristics

Ethnicity of participants was not made explicit in any of the studies. Out of the total 183 participants included in all three studies, 146 (80%) were female, with the mean (SD) age of the total sample (n=183) being 48.6 (9.4) years. No data was available on the range of participant ages in any of the studies, but none reported excluding participants on the basis of age. SES data was not well reported in any of the studies (Mills and Allen [289] described data on only half of their participants, of which half were in employment). The number of years in education was reported by Grossman et al. [177]. MS phenotype was outlined in two of the studies (Grossman et al. [177], and Mills and Allen [289]), with Tavee et al. [290] simply describing participants as having MS. Of the 166 participants in the Grossman et al. [177] and the Mills and

Allen [289] studies, 123 (or 67% of the total n 183) had RRMS, whilst 43 (or 25% of the total n 183) had SPMS. Excluded from all studies were those with dementia/severe cognitive impairment, those with severe physical disability (EDSS >6.0 i.e. maximally requiring two walking aids in order to walk 20 metres without rest), and more generally in the Mills and Allen [289] study if they could not make their own way to the hospital (Table 5.4).

Table 5.4 Participant characteristics

	Mills and Allen [289]	**Grossman et al**. [177]	**Tavee et al**. [290]
Ethnicity	NR	NR	NR
Number of participants (% **female**)	16 (80%)	150 (80%)	17 (78%)
Mean age (**SD**)	49.8 (6.8)	47.3 (10.3)	48.7 (11.2)
Socio-economic status	NR	NR	NR
Employment status	4 employed (25%)	NR	NR
Mean years of education (**SD**)	NR	14.1 (1.9)	NR
Disease phenotype	SP 16 (100%)	RRMS 123 (82%) SPMS 27 (18%)	NR
EDSS score	NR	Mean (SD) 3.0 (1.1)	Mean (SD) 3.0 (2.5)
Comorbidities	NR	NR	NR
Number taking disease modifying medication	NR	91 (60.1%)	NR
Number taking psychotropic medication	NR	30 (20%)	NR

1. SPMS - Secondary Progressive MS; 2. RRMS - Relapsing Remitting MS; 3. EDSS - Expanded disability status scale; 4. NR - Not recorded.

5.4.4 Outcomes

Perceived stress (the primary outcome of this review) did not feature in any of the included studies. Nevertheless, other secondary outcomes did, including anxiety, depression, fatigue, health-related QOL, and standing balance. There were no definitive data available for cost/benefit parameters or health service use (Table 5.2)

5.4.4.1 Mental health outcomes

5.4.4.1.1 Anxiety

Grossman et al. [177] used the Spielberger Trait Anxiety Index (STAI) to determine levels of anxiety. They demonstrated a significant reduction immediately following MBSR, both in the whole group, and in a sub-group analysis of those with levels indicating impairment pre-intervention. These findings remained significant at six-month follow up in both groups. However, in the Mills and Allen [289] study, anxiety as measured by a general MS symptom checklist and the Profile of Mood States (POMS), showed non-significant change over the period of study (Table 5.5).

5.4.4.1.2: Depression

The effect of MBIs on depression was assessed in the Grossman et al. [177] and the Mills and Allen [289] studies. In the Grossman et al. [177] trial the Centre for Epidemiological Studies - Depression scale (CES-D) demonstrated significant reductions in scores at post intervention in both the whole group, as well as in sub-group analysis of those with pre-intervention impairment. In both cases, this effect was maintained at six-month follow up. Similarly, Mills and Allen [289] reported a significant change in depression scores using the POMS (Table 5.5)

Table 5.5 Mental health outcomes

Study		**Outcome (Measure)**	**Post intervention effect size (p)**	**Follow up effect size (p) and time point**
Grossman et al. [177]	Full intervention group	Anxiety (STAI)	0.39 (0.0006)	0.36 (0.02) at six months
	Sub-group analysis		1.00 (0.002)	0.64 (0.05) at six months
	Full intervention group	Depression (CES-D)	0.65 (0.00001)	0.36 (0.03) at six months
	Sub-group analysis		1.06 (0.0002)	0.66 (0.03) at six months
Mills and Allen [289]		Anxiety (POMS)	$p > 0.05$*	$p > 0.05$*
		Depression (POMS)	$p < 0.01$*	NR

1.STAI - Spielberger Trait Anxiety Index; 2. CES-D - Centre for Epidemiological Studies Depression scale; 3.POMS - Profile of Mood States. * Effect size not recorded.

5.4.4.2 Physical outcomes

5.4.4.2.1 Standing balance

Mills and Allen [289] examined for change in scores for single leg standing balance. They noted improvements at study completion, and at three-month follow up, with only one individual's data missing (Table 5.6).

5.4.4.2.2 Pain

Tavee et al. [290] reported significant improvements in pain at the completion of their intervention, which used the Visual Analogue Scale (VAS) (Table 5.6).

5.4.4.2.3 Fatigue

Fatigue was measured in all three studies. Scores from the Modified Fatigue Impact Scale (MFIS) improved significantly after receiving MBSR training in the Grossman et al. [177] study, more so in those who had pre-intervention impairment. These effects were maintained at six-month follow up. In the Tavee et al, [290] trial significant pre-post beneficial changes on MFIS scores were also noted. However, in the Mills and Allen [289] study, fatigue was non-significantly improved, going by the POMS change scores (Table 5.6).

Table 5.6 Physical health outcomes

Study		**Outcome (Measure)**	**Post intervention effect size (p)**	**Follow up effect size (p) and time point**
Grossman et al. [177]	Full intervention group	Fatigue (MFIS)	0.41 (0.0001)	0.38 (0.001) at six months
	Sub-group analysis		1.27 (0.0005)	1.09 (0.02) at six months
Mills and Allen [289]		Fatigue (POMS)	$p > 0.05$*	NR
		Single leg standing balance	$p < 0.05$*	$p < 0.05$* at three months
Tavee et al. [290]		Fatigue (MFIS)	$p = 0.035$*	NR
		Pain (VAS)	$p = 0.031$*	NR
		PDDS	$p > 0.05$*	NR

1.MFIS - Modified Fatigue Impact Scale; 2.POMS - Profile of Mood States; 3.VAS - Visual Analogue Scale for pain; 4.PDDS - Patient Determined Disease Steps; 5.NR - Not recorded; *Effect size not recorded.

5.4.4.3 Psychosocial outcomes

In the Grossman et al. [177] study, both generic (Profile of health-related Quality of Life in Chronic disorders – PQOLC) and MS-specific (Hamburg Quality of life questionnaire in Multiple Sclerosis – HAQUAMS) QOL scores improved significantly, both in the group overall, and in those with levels indicating pre-intervention impairment. These effects persisted at six-month follow up. Mills and Allen [289] reported symptoms in general trending towards improvement (but without any statistical ratification), whilst Tavee et al. [290] did not report interpretable data for QOL from the Short From-36 (SF-36), with their results for people with MS being pooled with individuals with peripheral neuropathy (Table 5.7).

Table 5.7 Quality of life outcomes

Study		**Measure**	**Post intervention effect size (p)**	**Follow up effect size (p) and time point**
Grossman et al. [177]	Full intervention group	HAQUAMS	0.43 (0.0002)	0.28 (0.04) at six months
		PQOLC	0.86 (0.00000001)	0.51 (0.03) at six months
	Sub-group analysis	HAQUAMS	1.01 (0.0001)	0.58 (0.04) at six months
		PQOLC	1.71 (0.00000001)	0.51 (0.003) at six months

1.HAQUAMS - Hamburg Quality of Life Questionnaire in Multiple Sclerosis (German); 2.PQOLC - Profile of Health-related Quality of Life in chronic disorders (German).

5.4.5 Methodological quality

The Cochrane Collaboration tool for assessing Risk of Bias was employed to appraise study quality. Out of the included studies, Grossman et al. [177] were the only researchers to describe adequate sequence generation at the time of randomisation. They also most convincingly described allocation concealment, with the investigator blinded to participant information, whilst Mills and Allen [289] did not describe this clearly, and Tavee et al. [290] appear to have constructed a control group separately from those making up the intervention group (which comprised only those expressing a desire to be included in the intervention group). There was minimal suggestion of

incomplete outcome data reporting (to include attrition data), being described in all of the studies. However, only Grossman et al. [177] used attrition data and intention to treat (ITT) in the statistical analysis. Selective outcome reporting was not apparent in any of the studies. Using the Cochrane Collaboration guidance, only the study by Grossman et al. [177] can be considered of high methodological quality (Table 5.8).

Table 5.8 Risk of bias summary

	Grossmann et al. [177]	**Mills and Allen** [289]	**Tavee et al**. [290]
Random sequence generation (selection bias)	Low	Unclear	NA
Allocation concealment (selection bias)	Low	Unclear	NA
Blinding of assessors (performance bias)	Low	Unclear	High
Blinding of outcome assessment (detection bias) (patient reported outcomes)	High	High	High
Incomplete outcome data addressed (attrition bias)	Low	Unclear	High
Selective outcome reporting (reporting bias)	Low	High	Unclear
Other sources of bias (ie baseline bias)	Low	Unclear	Unclear

1.Low = Low risk of bias; 2.Unclear = Unclear risk of bias; 3.High = High risk of bias; 4.NA = Not available.

5.5 Discussion

This systematic review has examined the use of MBIs in people with MS, identifying only three eligible studies, which were heterogeneous in nature, only one study having the required statistical power to generate meaningful effect sizes. Rates of attrition were variable, with clear reasons seldom cited. The interventions did not all use the same methodology, two of the studies deviating from the standard MBSR protocol by including Tai Chi and Qi Gong as part of the mindful-movement elements. Furthermore, only two of the studies delivered the MBI in a group setting, whilst the remaining study administered the intervention on a one-to-one basis. The primary outcome in this current review was perceived stress, and it was not recorded

in any of the included studies, although other secondary outcomes of relevance, such as anxiety, depression, fatigue, standing balance, and QOL were.

Taken together these studies give encouraging results, in terms of mental health and health-related QOL effects. These beneficial effects (anxiety, depression, fatigue, health-related QOL) persisted for up to six months in the Grossman et al. [177] study, although effect sizes had diminished somewhat by that time. In the Mills and Allen [289] study, standing balance remained significantly improved by three-month follow up. No adverse events were reported in any of the studies.

5.5.1 Strengths and limitations of the review

A rigorous methodological approach was employed to undertake both the searching and appraisal of the literature examining the use of MBIs in people with MS. All screening and quality appraisal was undertaken by two independent reviewers, and a well-recognised and accepted tool was used (Cochrane Collaboration appraisal tool).

Given that MBIs originate from ancient Oriental roots, the fact that the review was necessarily (via budgetary constraints) limited to studies published in English may have introduced some bias. Meta-analysis was not deemed possible, given the heterogeneous nature of the studies, and the low methodological quality of two of the included studies compounded this situation further.

5.5.2 Strengths and limitations of included studies

The Grossman et al. [177] trial represents a well-designed RCT, which included a sufficient sample size (based on prior studies [14, 301]) to allow statistical power calculations and meaningful effect sizes. The authors' clear inclusion/exclusion criteria, and delivery of a standard manualised MBI, facilitated by certified and experienced trainers, with pre-,post-, and six-month follow-up measures, allows some confident inferences to be drawn from their findings. The Mills and Allen [289] and Tavee et al. [290] studies were not of such high quality, including smaller sample sizes, and opting for non-standard MBIs. Tavee et al. [290] did not randomise and employed a questionable control group.

Populations, interventions, and outcomes across the studies varied considerably. The effects of MBIs on different age groups in MS remains unclear, and how these might differ with respect to varied SES was not covered at all. Furthermore, information regarding MS phenotype, stage/severity of illness, the presence/absence of comorbidity was poorly characterised. Lastly, the dearth of data on economic costs/benefits precludes the drawing of any conclusions about the cost-effectiveness of MBIs amongst those with MS. Therefore, the results of this review should be treated with caution.

5.5.3 Implications for future research

From this review, it seems clear that future studies of MBIs for people with MS are needed to clarify a variety of unanswered questions. Studies might usefully seek information on a mix of physical and psychological measures pertinent to the MS population, and also more meaningful information on how MBI effects may differ with respect to different disease phenotypes, different stages of MS, amongst those with greater levels of disability, and across all relevant age groups. Important practical questions concerning feasibility, accessibility, and acceptability also need to be asked. Attrition rates varied widely in the above studies and it remains largely unclear why this might be. Qualitative research could seek specifically to provide answers to questions about accessibility, acceptability, and sustainability of MBIs for people with MS. Furthermore, it remains unclear as to how MBIs might fare amongst different ethnic groups, and ultimately if the intervention is cost-effective in those with MS. A final point to consider is whether MBIs need to be tailored for people with MS, given that levels of disability can vary considerably, as can disease activity, which is unpredictable, and disruptive [3, 62]. With this in mind, MBI trainers might themselves require enhanced training, and this too could be studied [217].

It would also be sensible for researchers to attempt to define the construct of mindfulness in any future studies in this area, and employ a validated measure in this regard. A range of measures is available [198], reflecting different definitions of the construct, such as the Mindful Attention Awareness Scale (MAAS) (measuring an integrated conceptual model [145]) or the Five-Facet Mindfulness Questionnaire (FFMQ) (reflecting proposed subcomponents of being mindful [131]).

Given that there may be a link between stress and MS exacerbation [8], future studies might examine for changes in perceived stress alongside specific biomarkers of inflammation. Using a contemporary biomedical model of stress [67], and correlating functional outcomes with disease biomarkers, such as via clinical imaging, could prove to be very useful in clarifying potential mechanism of action of MBIs in this group [302, 303].

5.5.4 Literature developments since completing the systematic review

Since this systematic review was completed, three further studies have been published examining the role of MBIs in people with MS. These will be briefly discussed here, but will be covered in full detail, in the same manner as those studies outlined in the present systematic review, in Appendix D.

In Germany, Burschka et al. [304] carried out a controlled trial, analysing data from 32 participants who took part in a MBI that focused mainly on mindful-movement, via Tai Chi. Participants were mainly RRMS patients (85%), and all had an EDSS<5.0. Outcomes focused primarily on balance, with secondary measures on QOL, fatigue and depression. Mindfulness was not measured. Amongst those receiving the intervention, significant improvements were noted for balance ($p<0.05$), co-ordination ($p<0.05$), depression ($p<0.05$), and QOL ($p<0.05$). Overall, this was a poor quality study, with multiple potential sources for bias.

In England, Bogosian et al. [305] undertook a RCT, randomising 40 people with progressive MS to receive a MBI based on MBCT for depression, but without mindful-movement, which was delivered ‘remotely’, via Skype. All levels of disability were eligible for participation, with the mean EDSS amongst participants 6.5. The primary outcome was distress, measured via the General Health Questionnaire (GHQ), and secondary outcomes measured mental health, fatigue, pain, the impact of MS symptoms, and likely cost-effectiveness. Mindfulness was not measured. Those who received mindfulness training had significant improvements in distress ($p<0.05$), anxiety ($p<0.05$), depression ($p<0.05$), the psychological impact of MS ($p<0.05$), fatigue ($p<0.05$), and the physical impact from MS symptoms ($p<0.05$).

In addition, a health economic analysis demonstrated likely effectiveness of the MBI, at a threshold of £20,000. Overall, for a pilot study this was of high quality, and adds important information on the potential use of MBIs in more disabled groups with MS.

In Iran, Kolahkaj and Zargar [306] carried out a RCT testing a MBI based on MBSR and MBCT in women with MS. Eligibility criteria were female sex and having any type of MS. Phenotype and disability level were not reported. Forty-eight women were randomised to receive the MBI or usual care. The primary and only outcome measure was the Depression, Anxiety, and Stress Scale-21 (DASS-21). Those completing the MBI demonstrated significant improvements in depression ($p<0.001$), anxiety ($p<0.001$), and stress ($p<0.001$) at post-intervention, and two months later. Reporting in this study was vague and overall methodological quality was low. The study does add useful information about the use of MBIs in another ethnic group.

5.5.5 Implications for clinical practice

This systematic review has reported findings that suggest that MBIs may have utility in people with MS, especially for mental health, for some physical aspects of MS, and for QOL. Developments since the review also suggest the potential for MBIs to be cost-effective in people with progressive MS. From the limited literature available, no overt evidence of harm from MBIs is apparent in this population.

5.6 Conclusions

The limited evidence that exists for the use of MBIs in people with MS suggests that they can be of benefit, especially in terms of mental health, some physical health measures, QOL, and possibly from a health economic perspective. Generalising these results to different ethnic groups, to include both sexes, diverse age groups, disparate disease phenotypes, and differing socioeconomic groups should be done with caution at this time. Whether MBIs might also benefit those with comorbidities and/or more severe disabilities is at present less clear. The next round of research needs to be of high methodological quality and may best employ a mixed-methods approach, in order to increase our understanding of barriers and facilitators to uptake, utilisation, and sustainability of such services.

Chapter 6 Randomised controlled trial – Mindfulness-Based Stress Reduction for people with multiple sclerosis versus wait list control

6.1 Summary

This chapter describes the research process and findings from a RCT of a MBSR intervention against wait-list control. The outline of the chapter is based on the CONSORT criteria for reporting RCTs [176]. The trial design and methods are described, followed by results, strengths and limitations, and interpretation of the findings in the context of the existing evidence for the use of MBIs in people with MS. Suggestions are then made for future research priorities, and how such questions might best be addressed.

6.2 Aims and objectives

The aim of this study was to test the feasibility and effects of conducting a RCT of a MBI for people with MS, and clarify whether a future definitive trial is currently merited. Specific objectives included:

- Assessing the feasibility of recruiting participants with MS to take part in a RCT of an eight-week MBSR course versus usual care
- To provide estimates of engagement (recruitment, retention, adherence)
- To assess the suitability of selected patient report outcomes and the feasibility of collecting these at baseline, immediately following MBSR, and three months later
- To evaluate the evidence of likely effectiveness of MBSR and determine variability estimates for selected outcome measures to inform power calculations for a definitive trial

6.3 Introduction

As discussed in Chapter 5, there are only a small number of studies from around the world (n=6) examining the use of MBIs in people with MS and these have left several questions unanswered. Such studies have, with the exception of Grossman et al. [177] (n=150), mostly included small sample sizes, with limited information provided about participant demographics, offering few details regarding ethnicity, SES, and other potentially important confounders such as the presence of comorbidities, on-going pharmacologic therapies, or previous exposure to meditation practices (see Chapter 5 and Appendix D). With one exception [305], trials have largely focused on participants who remain ambulant, and have not included more disabled people. Disability is common in MS, and thus there is a need to know whether or not more disabled individuals can engage with a MBI.

6.4 Materials and methods

6.4.1 Trial design and participants

This was a phase-2 RCT, designed to assess the feasibility (engagement and retention) and likely effects, if any, of MBSR on patient-reported outcomes in people with MS to inform decision making regarding the evidence to support a phase-3 trial. The trial employed a wait-list control design, in order to allow all study participants eventually to receive MBSR. The study was registered with Clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02136485), prior to any trial recruitment having taken place. Full ethical approval was prospectively granted via the NHS Lothian Research Ethics Council (REC reference number: 14/SS/0091) and NHS Greater Glasgow and Clyde (NHS GGC) acted as the host health board throughout (study ID number: GN14CH078). The protocol for this trial was made publicly available, prior to its commencement (http://www.gla.ac.uk/researchinstitutes/healthwellbeing/research/generalpractice/research/mbsr-ms/). The trial took place at the NHS Centre for Integrative Care (NHS CIC), Glasgow, a tertiary referral centre for Integrative Care services in Scotland.

Recruitment for the trial took place across Greater Glasgow NHS sites over a pre-specified three-month period during June – August 2014. Within this area, the Institute for Neurosciences (INS), the regional centre for MS care in the West of Scotland, formed the primary recruitment site, with the researcher (RS) attending weekly MS outpatient clinics. This was arranged following a meeting between the researcher and the Lead Clinician for MS services in the INS (Dr Stewart Webb). During their clinic reviews, the MS Specialist Nurses identified potential participants who were interested and eligible. These individuals were then further assessed by the researcher on-site, or at a later date, depending on patient preference. Secondary recruitment sites included the NHS CIC, MS Revive, and GPs in Greater Glasgow - all GP Practice Managers in Glasgow were contacted via e-mail and asked to distribute study flyer/clinician information sheets to GPs. Across these sites, all participants were recruited via NHS clinicians, including MS Specialist Nurses, Clinical Psychologists, Specialists in Rehabilitation Medicine, General Practitioners, and Specialists in Integrative Care (see Appendix E for an example of a Clinician Information Pack). Extended recruitment strategies also allowed for interested parties to get in touch with the researcher directly, for example if they had seen a study flyer, or heard about the study via word-of-mouth. Study flyers were posted at various NHS sites (INS, NHS CIC, Revive MS). Finally, the study was advertised online via University of Glasgow social media outlets on Facebook and Twitter, and also via the UK Multiple Sclerosis Society (MSS) website (http://www.mssociety.org.uk/).

As this was a feasibility study, no formal calculation for sample size was conducted. Browne [307] has demonstrated that a total sample size of 30 is sufficient to allow standard deviation (SD) estimates for outcome variables to determine sample size for an efficacy trial. Thus, sample size was determined based on this, but was also influenced by pragmatic reasoning; namely that the maximum group size which the NHS CIC could accommodate was 25 participants per class. Thus, a recruitment target of 50 people i.e. two groups of 25 was set. Box 6.1 delineates eligibility criteria.

Initial screening for eligibility of potential participants took place through NHS clinicians, but also by the researcher in every case. Prior to meeting, potential participants were sent out detailed information regarding the study aims and

objectives, and scientific rationale – see Appendix F. In all cases it was made clear that this was a feasibility study. The face-to-face meeting between the researcher and potential participants allowed the following to be completed:

1) Addressing any remaining doubt about eligibility
2) Collection of informed consent
3) Baseline measures on the participant questionnaire, including assessment of disability level using the EDSS score [117].

Box 6.1 Eligibility criteria

Inclusion criteria	Exclusion criteria
1) Over 18 years of age; 2) Neurologist confirmed diagnosis of MS; 3) Able to understand spoken and written English; 4) A score of less than or equal to 7.0 on the EDSS* to allow for active participation in the Hatha Yoga asana postures	1) Life-threatening physical or mental health conditions, such as suicidal ideation, active psychosis, or terminal/life threatening inter-current medical illness, or such conditions expected to limit significantly participation and adherence, including dementia, pregnancy, ongoing substance abuse; 2) Those currently receiving another form of psychological intervention (non-pharmacological).

* EDSS = Expanded Disability Status Scale [117]. Score of 7.0 = '*Unable to walk beyond approximately 5 metres, even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day'*

A priori stopping criteria were for trial discontinuation in the occurrence of any adverse event(s) strongly suggesting harm derived from the intervention.

Recruited participants had baseline measures and informed consent collected face-to-face with the researcher, prior to randomisation. Follow-up measures were collected by post, at intervention completion (i.e. two months) and then again three months later (i.e. at the five-month point). Those who did not return postal measures within 14 days were telephoned to confirm their on-going participation and encourage their self-completion of the questionnaire. Participants received a £5 gift voucher as a gesture of appreciation for their completing each cycle of the questionnaire.

6.4.2 Randomisation

A member of staff who was not involved in recruitment (Suzanne Lloyd - SL) at the RCB, University of Glasgow, undertook a random sequence generation procedure. The statistician generated a list in blocks of two, so as to minimise the risk of over-allocation into the two groups, where a maximum of 25 participants could not be exceeded due to space constraints. SL had no prior knowledge or way of identifying any of the individuals in the trial and simply allocated a random number to each participant. The numbered list was then passed to a blinded member of administrative staff (John McLeod – JM) in General Practice and Primary Care (GPPC) at the University, who otherwise had no part in the trial or PhD project. JM then contacted all participants to inform them of their group allocation. JM also fielded calls from participants relating to attendance and attrition. Follow-up measures were all identified according to participant number. Blinding of participants and care providers was not possible, given the nature of the intervention. The researcher remained blinded to allocation and undertook data entry for the first and subsequent iterations of the questionnaires. All forms were anonymous, and were returned to the researcher with only a unique numerical identifier on their outer cover.

6.4.3 Statistical analysis

In association with RCB staff (SL), an a priori statistical analysis plan was developed and made publicly available in advance of all data being collected: http://www.gla.ac.uk/researchinstitutes/healthwellbeing/research/generalpractice/research/mbsr-ms/

To assess the feasibility, acceptability and accessibility to patients with MS, key outcomes included recruitment and retention. These were calculated by descriptive statistics reporting frequencies and percentages.

Baseline characteristics were summarised according to intervention arm.

Differences between the arms were tested using two-sample ‘t’-tests for normally distributed variables, and chi-square tests for categorical variables.

Questionnaire outcome data were analysed in relation to change from baseline using an Analysis of Covariance approach (ANCOVA), adjusting for the baseline score, as appropriate. ANCOVA is an extension of analysis of variance (ANOVA), measuring spread of data points away from the mean – the square of the SD. It compares two means amongst two or more groups to assess whether they derive from the same population. ANCOVA permits the model to include continuous variables, for example, any variable which can fall anywhere within a range of values e.g. weight, height etc [167]. Models were adjusted for age, sex, and deprivation, as well as any characteristics found to differ between the intervention arms at baseline. Based on advice from the statistician (SL), no plans were made to impute missing values, although these would be subject to scrutiny later on in the analysis, and reported as part of the overall assessment of feasibility. No interim analyses were undertaken. All statistical analyses were carried out using SPSS v21.

For questionnaire data, study results are reported for between group mean (SD) baseline scores, change scores, treatment effects (β), 95% confidence intervals, significance levels, and effect sizes (ES - Cohen's 'd').

6.4.4 Intervention

Two experienced physician instructors delivered the intervention:

1. Dr Leonora Coll had a clinical background in General Practice since 1983 and at the time of the RCT worked full time as a Specialty Doctor in Integrative Care at the NHS CIC. Dr Coll had completed teacher training in MBCT in 2005, via the University of Bangor, and had been teaching mindfulness since then. In addition, she had completed residential MBSR training in with Jon-Kabat-Zinn, in the USA in 2011, along with regular attendance at training retreats in MBCT and Vipasana meditation around the world. She had a teaching qualification in Iyengar Yoga and in Pranayama. She regularly attended one-to-one clinical supervision for her mindfulness teaching and had a longstanding daily practice.

2. Dr Bridie O'Dowd also had a background in General Practice, completing her training in 1994. She qualified as a mindfulness teacher in 2011, again via the University of Bangor. At the time of the RCT, she was halfway through completing an MSc qualification in teaching MBIs via the University of Bangor. She also had a longstanding daily mindfulness practice and undertook regular clinical supervision.

The mindfulness teachers had been working together to deliver courses at the NHS CIC for three years. Both took time to prepare for delivering the course in this study. Their preparations included meeting with the researcher to discuss the RCT, liaising with nursing, physiotherapy, administrative, and management staff at the NHS CIC, arranging room booking for the course, and meeting with each other to discuss the course in general prior to its commencement, and then prior to each mindfulness session to prepare, including reviewing comments made on participant home practice sheets that had been returned the week previously. In addition, both instructors met at the end of each mindfulness session to debrief with one and other.

The intervention was based on the most widely used, manualised form of MBSR [13] (Appendix G). The only 'modification' was omission of the full day-retreat at week six. The decision to exclude this component was based mainly on resource constraints, namely that the NHS CIC operates at near to full capacity throughout the week, and is not open at the weekends, but was also supported by the fact that very little evidence exists to suggest that the day retreat is an essential component [308].

The control group received whatever they normally would do via standard NHS patient contacts, such as making appointments with their GP, MS Specialist Nurse, or Consultant in Rehabilitation or Neurology, as required. However, no attempt was made to characterise this further during the trial. At the time of recruitment into the trial, all participants (regardless of eventual assignment to intervention or control) had received a participant information pack that described trial procedures, including the purpose of the study, why they had been chosen to take part, what would happen if they took part, what mindfulness was, including core components, session lengths, expectations regarding attendance on the course, home practice requirements, questionnaire length and estimated completion time, the likelihood of being invited

for a qualitative interview following MBSR. All were made aware that everyone would eventually receive MBSR (Appendix F).

Relatively high levels of disability were considered a strong possibility from the outset, given that this trial sought to include participants with higher EDSS (disability) scores than those in previous studies that had been identified via the systematic review (Chapter 5 and Appendix D). Despite this, there were no initial changes made to any of the core MBSR practices of mindful-breath-awareness, mindful-body-awareness, or mindful-movement. However, the importance of flexibility in application of the practices was agreed in advance with the MBSR instructors, with provisions made for the possibility of recruiting skilled NHS CIC moving-and-handling trained nursing staff into the group setting, should their expertise be required.

6.4.4.1 Intervention fidelity

No explicit measures were put in place to measure intervention fidelity during the study, such as video recording of sessions, or having an independent reviewer 'sit-in' on MBSR classes etc [178]. The decision not to do so was made based on the MRC guidance [19], which suggests that this may be impractical in a feasibility trial, more so when it was limited to a single study site, with the same MBSR instructors delivering the intervention throughout, both of whom were used to working with each other in this capacity. The decision was also based on the anticipation that, as this was a feasibility study, protocol deviation might be necessary i.e. to accommodate a more disabled group. It was also influenced by practical, time, and resource constraints associated with the PhD. However, if the guidance suggested by Bellg et al. [178] for measuring fidelity in behavioural interventions is considered, then fidelity was indirectly measured in a number of other ways during this study - see Table 6.1 below.

Table 6.1 MBSR treatment fidelity

Fidelity domain	How it was met
1. Study design	Use of an a priori study protocol; a fixed number and length of MBSR classes; protocol deviations recorded; manual for course scripted (MBSR); external monitoring from research team and another MBSR instructor who was not part of the research project; home practice monitoring
2. Provider training	By using qualified and experienced mindfulness instructors; instructors trained together using scripted MBSR treatment manuals; use of the same instructors throughout; external provider debriefing and supervision for instructors on a regular basis; access to senior research staff (SM) freely available; exit interviews for participants enquiring about the course content
3. Improving delivery of MBSR	Qualitative assessments from participants undertaken regarding provider 'warmth/credibility', complaint monitoring in situ; course reading provided to all participants ('Full Catastrophe Living');
4. Improving receipt of MBSR	Weekly participant feedback encouraged by instructors, both in writing (embedded questionnaire – not part of study data), and verbally; regular activity logs completed by participants; feedback from participant and providers on MBSR exercises during classes; follow-up with drop-outs via telephoning by instructors
5. Improving MBSR skill enactment	Semi-structured participant interviews on completion of MBSR; home practice and materials provided regularly along with a diary for adherence measurement; in class discussion and post-MBSR interview discussion on on-going use of MBSR skills in their daily life

The MRC guidance [19] helped the researcher to consider how best to minimise deviation from the standard MBSR package. For example, both instructors were trained and competent to deliver MBSR specifically. The researcher met with both instructors on a number of occasions prior to the study taking place, in order to gain consensus on course content, which was based on the MBSR manual produced by the University of Massachusetts Center for Mindfulness. It was also agreed with the researcher's supervisors (SM, FM), that any deviations in the protocol, intended, or otherwise, would be recorded as part of the evaluation process. Lastly, it was anticipated that the parallel process evaluation using qualitative semi-structured interviews from participants and instructors, and an implementation analysis would likely yield useful information pertaining to intervention fidelity, in terms of course structure and components.

6.4.5 Study outcomes

6.4.5.1 Primary feasibility outcomes

With respect to primary outcomes, there were three main objectives:

1) To see if MBSR was feasible i.e. was it possible to recruit, to randomise, to deliver the intervention, and to retain participants in the study?
2) To determine the suitability of the outcome measures chosen
3) To establish whether it was possible to collect outcomes measures at baseline, post-intervention, and at three-month follow-up?

Feasibility outcomes were considered for the following:

- Reaching the recruitment target of 50 participants
- Consent rates
- Refusal rates
- Study questionnaire length, content, and missing-ness
- Adherence rates to course sessions and home practices
- Course completion rates

The main outcome measures were self-report, and reflected the interest in the relationships between stress, MS, and QOL.

6.4.5.2 Primary patient outcomes

The main objectives for primary patient outcomes were to assess the likely effectiveness of MBSR training for reducing scores of perceived stress and for increasing scores for QOL. Perceived stress was assessed via the ten-item Perceived Stress Scale (PSS-10) [185]. QOL was measured via the EQ-5D-5L. Both of these measures have been used previously in studies examining the stress-modulatory effects of meditation amongst people with MS, Pritchard et al. [127] using the PSS-10; Bogosian et al. [305] using the EQ-5D-5L

- The PSS-10 is a measure of the individual's perception of how stressful life events have been over the past four weeks. The PSS-10 has the best

psychometric properties (internal consistency) in patients with MS, as compared to the longer (14-item) or shorter (four-item) versions [186]. Originally designed as a single construct measure [184], recent evidence suggests that a two-dimensional construct is more likely for the PSS-10; one relating to perceived stress (assessed via items 1,2,3,6,9,10 on the scale), and one to stress resilience (items 4,5,7,8, which are reverse-scored) [183]. The author of the scale [185] describes it as being designed to ascertain how overloaded, uncontrollable, and unpredictable respondents find their lives. The range of scores that a respondent may return vary between 0-40, with higher scores indicative of higher perceived stress. Higher scores have been associated with a greater vulnerability to depressive symptoms and/or viral infections following SLEs. In general, it is recognised as having good psychometric properties, with a Chronbach's-α reliability co-efficient of 0.89, and it also has supportive convergent/divergent validity [309]. A limitation is that it does not have a cut-off score indicative of clinical significance, but normative values in US populations are described as mean (SD) scores of 12.1 (5.9) for males, and 13.7 (6.6) for females [184]. In Danish samples, a level over 18.0 is considered to indicate abnormally high stress [50].

- The EQ-5D-5L is a generic two part self-report measure of QOL, which aims to capture data on physical, mental, and social functioning [188]. The first part relates to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These can be scored as having no problems, slight problems, moderate problems, severe problems, and extreme problems. The second part is a scale 0-100, asking the respondent to rate their state of health. The EQ-5D-5L has been validated in diverse patient populations with chronic conditions in many different countries around the world, and has been shown to have good test-retest reliability in UK populations [188]. Participant responses are converted into a numerical score that has been weighted for diverse populations around the world based on population norms so that it can be calculated as a single utility score. The utility score can then be used as part of a health economic analysis. In this study, scores were converted to UK weighted values: http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html

6.4.5.3 Secondary patient report outcomes

Secondary patient report outcomes were chosen to cover the impact of common MS symptoms, the putative mechanisms of action for MBSR, and emotional lability.

The Multiple Sclerosis Quality of Life Inventory [191] (MSQLI) was chosen as a composite measure to represent the variety of symptoms and issues known to be prevalent in people with MS i.e. physical, mental, and social problems. This measure was specifically designed for and validated in people with MS, across a range of ages, and including those with cognitive impairment [191-193]. Prior to this study, the MSQLI had been used almost exclusively in North American populations, and never within Scotland. Construct validity, internal consistency and reliability have been reported as adequate, with only the vision scale being less reliable in those with cognitive impairment [191, 192].

The MSQLI includes the option of using another generic QOL score, the Health Status Questionnaire, Short-Form 36 (SF-36). The SF-36 was not used in this present study for three reasons: a) the EQ-5D-5L was already being used as a generic QOL measure b) the questionnaire was already 27 pages long, with an estimated toil time of 45-60 minutes, and c) the SF-36 came with a copyright, requiring payment for usage. Thus, the SF-36 component of the MSQLI was omitted from the participant questionnaire.

The MSQLI measures scores for items over the last four weeks, covering:

- Fatigue – The Modified Fatigue Impact Scale (MFIS) has 21 separate items, designed to measure how much cognitive (items 1,2,3,5,11,12,15,16,18,19), physical (items 4,6,7,10,13,14,17,20,21), and psychosocial (items 8,9) aspects of fatigue have impacted on daily activities. It has an internal consistency reliability Chronbach-α of 0.96. Higher scores indicate a greater impact of fatigue [191]
- Mental health – The Mental Health Inventory (MHI) is an 18-item questionnaire, measuring four separate domains, covering anxiety (items 4,6,10,11,18), depression (items 2,9,12,14), behavioural and emotional control

(items 5,8), and positive affect (1,7,13,15). These four facets are different factors and are scored separately [191]. Items 1,3,5,7,8,10,13,15 are reverse scored, and higher scores are indicative of better mental health.

- Cognitive function – Impact of subjective cognitive dysfunction is measured by the 20-item Perceived Deficits Questionnaire (PDQ), which assesses aspects of attention/concentration (items 1,5,9,13,17), retrospective memory (items 2,6,10,14,18), prospective memory (items 3,7,11,15,19), and planning/organisation (items 4,8,12,16,20). Higher scores indicate a greater subjective cognitive deficit. It has an internal consistency reliability Chronbach-α of 0.93 [191].
- Social support – The Modified Social Support Survey (MSSS) is an 18-item questionnaire assessing tangible support (items 1,4,11,13), emotional support (items 2,3,7,8,12,14,15,17), affective support (items 5,9,18), and positive social interaction (items 6,10,16). It measures patient-perceived social support. Higher scores indicate higher perceived social support. It has an internal consistency reliability Chronbach-α of 0.97 [191].
- Pain – This is assessed via a six-item, modified version of the Medical Outcomes Study Pain Effects Scale (PES). Pain is defined as '*any unpleasant sensory symptom related to MS*'. It is designed to assess the effects of pain on mood and behavior, with higher scores reflecting higher impact. It has an internal consistency reliability Chronbach-α of 0.89 [191].
- Visual function – The five-item Impact of Visual Impairment Scale (IVIS) assesses how much vision-dependent activities that are not correctable with visual aids are affected by MS-related visual dysfunction. It has an internal consistency reliability Chronbach-α of 0.87 [191]. Higher scores represent greater visual dysfunction affecting daily activities.
- Bladder function – This is examined via the four-item Bladder Control Scale (BCS). It has an internal consistency reliability Chronbach-α of 0.84 [191]. Higher scores indicate greater dysfunction.
- Bowel function – This is assessed via the five-item Bowel Control Scale (BWCS). This scale has an internal consistency reliability Chronbach-α of 0.76 [191]. Higher scores indicate greater dysfunction.

- Sexual functioning and sexual relationships – This is assessed via the four-item Sexual Satisfaction Scale (SSS), which has an internal consistency reliability Chronbach-α of 0.92 [191]. Higher scores indicate less satisfaction/more problems in this area.

The next set of secondary patient report outcome measures focused on the putative processes of mindfulness. They included the Mindful Attention Awareness Scale (MAAS) [145] and the Self-Compassion Scale-short Form (SCS-sf) [201].

- The MAAS is a generic single construct measure of mindfulness, designed to capture data on present-centred awareness, or the 'presence/absence' from everyday experiences. It has 15 items, and can be used by the novice or experienced practitioner alike. The MAAS has been reported as having good internal consistency (with a Chronbach-α of 0.78-0.92), test-retest reliability, and construct validity, with weak-moderate correlations with other commonly used measures of mindfulness [198]. Higher scores indicate higher levels of mindfulness, and more experienced meditators have been found to score more highly than novice counterparts [198]. Normative levels in community adults have a mean value of 4.20 (SD 0.69) [145].
- Neff [202] describes the construct of self-compassion as *'..the ability to hold one's feelings of suffering with a sense of warmth, connection, and concern*.', with the construct having three key components: 1) kindness – treating oneself with care, 2) common humanity – recognising the universality of imperfection in human experiencing, and 3) mindfulness – a balanced perspective. Six second-order components are assessed via the questions in the SCS-sf (I. common humanity – items 5,10; vs. II. isolation – items 4,8; III. mindfulness – items 3,7; vs. IV. over identification – items 1,9; and V. self-judgement – items 11,12; VI. vs. self-kindness – items 2,6) [201]. The SCS-sf is a 12-item scale that asks participants to score their experiences from 1-5, with items covering self-judgement, isolation, and over-identification being reverse scored. Higher overall scores indicate being more compassionate towards one's self. Originating from the Netherlands, it has been validated in English, with adequate internal consistency and reliability, having a Chronbach-α of

0.86. Mean (SD) normative values in clinical populations are quoted as 2.80 (0.74) [201].

Finally, given that difficulties with emotional regulation are commonly described amongst people with MS, a measure of emotional lability was also included. At the time of protocol development, the researcher was not aware of any validated scale for measuring emotional lability in people with MS. Following a combination of literature searching and discussion with expert neuropsychology clinicians in the field (Dr. Niall Broomfield, NHS GGC), the Emotional Lability Questionnaire (ELQ) [194] was chosen.

- The ELQ was originally designed for use in people with Motor Neurone Disease (MND), another neurodegenerative condition with some features similar to MS, including high levels of emotional lability [194]. Adapting this scale for people with MS involved discussing its use with the scale authors', who suggested simply substituting in the term 'MS' to replace MND in scale items numbered: 11, 22, and 33. The ELQ has 33-items, and is described by its authors as having confirmed internal consistency, particularly in cases of pathological emotional lability [194]. There was very little psychometric data on the ELQ in the literature, aside from one validation study in Italian MND patients [195].

Data was also collected on a range of demographics including age, sex, education, SES, disease duration, level of disability (EDSS), comorbidities, drug usage including DMDs, analgesics, and psychotropics, and previous exposure to meditation and/or yoga. All participants completed the initial questionnaire with the researcher in attendance, in order that any practical problems, or difficulties interpreting the questions were identified and addressed at this early stage. Subsequent follow-up questionnaires were posted out to participants to complete on their own immediately post-intervention, and then again three-months following completion of the intervention.

6.5 Results

6.5.1 Baseline data

Table 6.2 (below) summarises baseline data for participants allocated to MBSR versus the control group. At baseline, mean age (SD) for the total sample was 44.96 (10.90). Participants were predominantly female (n=46, 92%), most being White Scottish (n=49, 98%). Phenotypic breakdown included 40 people with RRMS (80%), eight (16%) with SPMS, and two (4%) with PPMS. Intervention and control groups were similar at baseline, with respect to age, sex, and SES, and the only significant difference between the groups related to previous exposure to meditation and/or yoga practice. For this reason, previous meditation/yoga experience was also controlled for in the adjusted analyses.

Table 6.2 Baseline characteristics

	Intervention	**Control**	**Significance p**
Mean age in years (standard deviation - SD)	43.6 (10.7)	46.3 (11.1)	0.37
Sex	Female 23 (92%)	Female 22 (88%)	1.00
Ethnicity	White British 25 (100%)	White British 25 (100%)	1.00
MS phenotype RRMS – relapsing remitting; SPMS – secondary progressive; PPMS – primary progressive	RRMS 22 (88%) SPMS 1 (4%) PPMS 2 (8%)	RRMS 18 (72%) SPMS 7 (28%)	0.74
Deprivation decile	5.0 (2.8)	5.4 (2.6)	0.64
Education – highest level	Secondary school 3 (12%) College 7 (28%) University 15 (60%)	Secondary school 5 (20%) College 7 (28%) University 13 (52%)	0.73
Employment	Full time 4 (16%) Part time 3 (12%) Unemployed 6 (24 %) Retired 5 (20%) Other 7 (28%)	Full time 7 (28%) Part time 6 (24%) Unemployed 7 (28%) Retired 3 (12%) Other 2 (8%)	0.39
Living arrangement	Lives alone 6 (24%) With partner 9 (36%) With family/friends 10 (40%)	Lives alone 3 (12%) With partner 10 (40%) With family/friends 12 (48%)	0.54
EDSS	4.5 (1.8)	4.3 (1.7)	0.64
Mean disease duration in years (SD)	8.9 (8.5)	9.6 (9.4)	0.79
Mean total comorbidity count (SD)	2.5 (2.2)	2.3 (1.9)	0.68
Mean mental health comorbidity count (SD)	0.8 (0.83)	0.7 (0.8)	0.73
Mean physical health comorbidity count (SD)	1.8 (1.5)	1.6 (1.5)	0.71
Using analgesic drugs	19 (76%)	17 (68%)	0.75
Using disease modifying drugs	14 (56%)	12 (48%)	0.78
Using psychotropic drugs	12 (48%)	11 (44%)	1.00
Previous meditation/yoga experience	17 (68%)	10 (40%)	***0.04***

6.5.2 Primary feasibility outcomes

6.5.2.1 Patient recruitment and retention in the trial

In total 101 patients were approached via the different recruitment sites. From this overall number, 66 (65%) contacted the researcher (RS) and were screened. After screening, three people were deemed ineligible (EDSS>7.0), whilst 13 decided at that stage not to take part for the following reasons: difficulties securing transport (n=7), difficulties getting time off work (n=4), perception the course would be too tiring (n=1), and for unclear reasons in the remaining person. The consent rate was thus 50/66, or 76%. Thus the original recruitment target of 50 people was met. These individuals were recruited and completed baseline measures, before being randomised to receive either the MBSR intervention, or to go on to a wait list control group, where they would continue to complete measures at the same time points as those receiving MBSR.

Recruitment to the target n of 50 was completed by week 10, out of the pre-specified 12 weeks (Table 6.3).

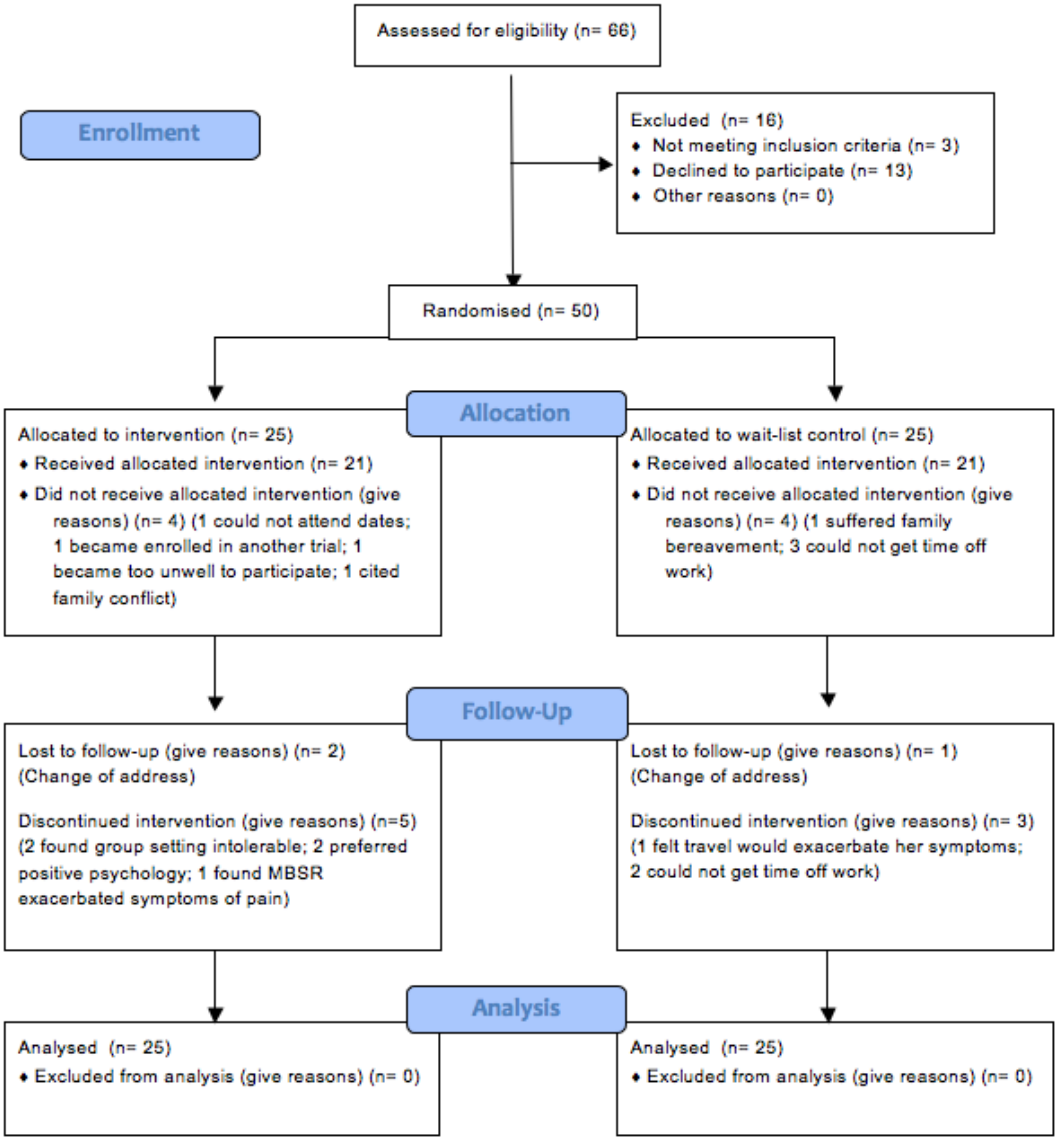
No index entries found.**Table 6.3 Sources of trial recruitment**

Source of engagement/ recruitment	Numbers known to have been approached	Numbers (known) expressing interest	Numbers recruited into trial (n/50)	Percentage of recruitment overall
MS Specialist Nurses	75	52	34	68%
MS Revive Nurse	6	6	6	12%
Integrative Medicine Specialists	9	9	5	10%
General practitioners	11	11	5	10%
Via MS Society advertisement	Freely available online	2	0	0%
Via University web (Twitter/ Facebook)	Freely available online	0	0	0%
Via protocol (clinical trials.gov)	Freely available online	5	0	0%
Total	101(+)	85	50	N/A

6.5.3 Participant flow

The flow of participants throughout this study is detailed in the following CONSORT flow diagram (Figure 6.1)

Figure 6.1 CONSORT flow diagram



For all participants, measures were taken at baseline during the three-month recruitment window prior to the first MBSR course commencing, at the end of the first MBSR course at two-months, and then at follow-up, a further three months later. All 50 participants completed baseline questionnaire measures with the researcher present, requiring minimal assistance. Despite initial concerns that the length of the

questionnaire might be too long for participants, a pilot sample of the first five participants completing it identified no such issue, so the decision was made to stick with the full-length version throughout the study. At the post-intervention time point, 45/50 (90%) participants returned the questionnaire measures by post. In two cases, measures had to be re-sent, having become lost in transit. At follow-up (three months following the completion of the MBSR course) the number of participants returning measures had only dropped slightly to 44/50 (88%). Facilitating this high level of return necessitated several telephone reminders to participants, with an average number of 4.4 telephone calls per person, and 222 in total. Retention rate in the study varied from 90% immediately post-intervention, to 88% three months following MBSR.

Missing values varied considerably across the measures and time points. Twelve of the 14 measures accrued levels for missing values below 20%, with the lowest levels being for the EQ-5D-5L (0-12%), and the highest levels being seen for the SCS-sf (2-22%). For full details regarding missing values, see Appendix H.

6.5.3.1 Treatment adherence

Adherence to treatment was defined by how closely participants followed their prescribed practices for the MBSR treatment [310]. In this study, this was measured via MBSR session attendance and self-reported home practice completion rates.

Of those allocated to the intervention, only 21 out of 25 (88%) were able to attend any of the MBSR classes. From the four who did not attend any of the classes, reasons reported for not taking part included: not wishing to be allocated to MBSR at the first iteration, where the later course dates suited better; becoming involved in another MS trial with a pharmacological intervention; becoming too unwell to participate; and experiencing family conflict. Four people (16%) only attended one session, with reasons cited for not coming back as: having expected the course to be one-to-one therapy (n=1), or not liking the mindfulness approach (n=2). One participant could not be contacted following his departure from the course, but feedback from his MS Specialist Nurse suggested his leaving was due to social anxiety. Reasons accounting for non-attendance are highlighted in Figure 6.1.

For those continuing to attend the classes, reasons cited for non-attendance at individual MBSR sessions varied, from difficulty getting up on time; transport difficulties; problems arranging childcare; work commitments; inter-current illness including MS relapses, or having a cold; to being on holiday. For a detailed breakdown of MBSR attendance, see Table 6.4 below:

Table 6.4 MBSR session completion rate

MBSR sessions completed	Number of participants	Percentage (%)
All	3	12%
7	8	32%
6	3	12%
5	1	4%
4	0	0%
3	1	4%
2	1	4%
1	4	16%
0	4	16%

From the 25 participants allocated to MBSR there was a completion rate of 60% (15/25). This is adjudged via a cut-off value of four or more MBSR sessions being taken as a minimum attendance for 'completion' of the course [197, 311, 312].

From those 25 participants initially allocated to the control arm, four dropped-out of the course altogether, one citing family bereavement, and the remaining three not being able to get time off work.

In terms of home practice adherence, all MBSR participants were routinely asked to do this for the duration of the course. However, only 16 participants returned figures in this regard, and from their responses this generated an average practice time of 32.5 minutes/day.

6.5.3.2 Protocol deviations

The only deviation that was necessary related to mindful-movement, which had been anticipated as a possibility during the pre-trial development stage in discussions with the MBSR instructors. In the event, the MBSR instructors responded reflexively to

the perceived needs of the group, in terms of their level of physical disability and how they were responding to the practices during the course. This was in keeping with their usual practice for delivering mindfulness courses. However, despite this, the level of disability encountered by the MBSR instructors, along with participant responses to the practices, led to the instructors having to adapt more extensively than they had anticipated, in order that they meet the needs of the group. Thus, following the first few MBSR sessions, discussion took place with an experienced physiotherapist/ mindfulness teacher at the NHS CIC, and based on this a simplified version of the movement practice was administered subsequently that allowed engagement from a seated position, to include head movements, hand movements, wrist rotations, shoulder rolls, shoulder circles, arm movements, and foot slides.

6.5.3.3 Adverse events

One participant allocated to the intervention group reported an exacerbation in her symptoms of neuropathic pain following her first, and only class. This is reported in greater detail in the qualitative research chapter.

6.5.4 Outcomes and Estimation

There were no significant differences between the groups on any of the baseline outcome measures. The models presented below are adjusted for age/sex/deprivation/previous yoga/meditation experience. For unadjusted models, see Appendix I. Overall, in the models adjusted for age, sex, SES, and previous meditation/yoga experience, at the immediate post-intervention point, 14 out of 15 patient outcomes showed a positive trend for treatment effects from MBSR (Figure 6.2). At follow-up (three-months after the end of the course), 14 out of the 15 patient report outcomes showed a trend towards improvement (Figure 6.3). These findings are explained further below in terms of primary and secondary outcomes.

6.5.4.1 Primary patient outcomes

6.5.4.1.1 Post-intervention

Immediately post-MBSR, scores on the Perceived Stress Scale-10 (PSS-10) were improved in the treatment group with a large effect size (ES 0.93; 95%CI 0.41 – 1.44; p<0.01). These improvements post-MBSR were large for both the items on the PSS-10 representing a decrease in the negative aspects of perceived stress (ES 0.82; 95%CI 0.29 – 1.34; p<0.05); and for those items measuring stress resilience (ES 0.92 95%CI 0.40 – 1.45; p<0.05) (Table 6.5). From the overall PSS-10 baseline scores, the changes noted in the treatment group are likely to be clinically significant, with a reduction from abnormally high stress scores (>18) to those approximating normative levels (12-13).

Effect sizes for QOL on the EQ-5D-5L scores were very small at post-MBSR in both un-weighted (ES 0.13; 95%CI -0.48 – 0.74; p=0.66), and weighted scores (ES 0.17; 95%CI -0.3 – 0.61; p=0.48), and negligible on the Area-Under-the-Curve (AUC) analysis (ES 0.00; 95%CI -0.50 – 0.75; p=0.80). On the EQ-5D-5L subscales, the largest effect size was found on the subscale for anxiety/depression (ES 0.41; 95%CI -0.16 – 0.90; p=0.16), with negligible effect sizes found on subscales for mobility (ES 0.07; 95%CI -0.60 – 0.73; p=0.85), pain/discomfort (ES 0.05; 95%CI -0.63 – 0.52; p=0.86), self-care (ES 0.03; 95%CI -0.65 – 0.58; p=0.92), and usual activities (ES 0.01; 95%CI -0.59 – 0.57; p=0.97) (Table 6.6).

6.5.4.1.2 Three-month follow up

At three-month follow-up, the effect size favouring MBSR for overall PSS-10 scores was small (ES 0.26; 95%CI 0.26 -0.37 – 0.85; p=0.39). The effect size in favour of MBSR was very small for items measuring the negative aspects of stress (ES 0.12; 95%CI -0.52 - 0.77; p=0.71), but was somewhat higher for items measuring stress resilience (ES 0.46; 95%CI -0.01 – 0.91; p=0.05) (Table 6.5).

Effect sizes for improvements in EQ-5D-5L QOL favouring MBSR were small for un-weighted values (ES 0.23; 95%CI -0.43 – 0.89; p=0.48), and very small for weighted values (ES 0.08; 95%CI 0.35 – 0.50; p=0.71), and on the AUC analysis (ES 0.10; 95%CI -0.50 – 0.80; p=0.71). Once again, on the EQ-5D-5L subscales the largest effect size favouring MBSR was on the anxiety/depression subscale (ES 0.26; 95%CI -0.38 – 0.90; p=0.42), with very small effect sizes evident on scores for usual activities (ES 0.12; 95%CI -0.51 – 0.74; p=0.69), mobility (ES 0.11; 95%CI -0.78 –

0.53; p=0.70), self-care (ES 0.10; 95%CI -0.52 – 0.70; p=0.77), and pain/discomfort (ES 0.06; 95%CI -0.57 – 0.69; p=0.85) (Table 6.6)

6.5.4.2 Secondary patient outcomes

6.5.4.2.1 Post intervention

At the post-MBSR time point, improved scores favouring the intervention were evident on a number of the MSQLI measures (Table 6.7). Medium magnitude effect sizes were evident for the Sexual Satisfaction Scale (SSS) (ES 0.70; 95%CI -0.20 – 1.60; p=0.12), the Modified Fatigue Impact Scale (MFIS) (ES 0.63; 95%CI -0.02 – 1.12; p=0.06), and the Mental Health Inventory (MHI) (ES 0.54; 95%CI -0.03 – 1.10; p=0.06). Smaller effect sizes were evident on the Pain Effects Scale (PES) (ES 0.44; 95%CI -0.14 – 1.01; p=0.13), the Perceived Deficits Questionnaire (PDQ) (ES 0.43; 95%CI -0.15 – 1.02; p=0.14), and the Impact of Visual Impairment Scale (IVIS) (ES 0.30; 95%CI -0.23 – 0.82; p=0.26). Very small effect sizes for improvement were also discernable on scores for the Bowel Control Scale (BWCS) (ES 0.16; 95%CI -0.41 – 0.72; p=0.58) and the Bladder Control Scale (BCS), (ES 0.13; 95%CI -0.41 – 0.68; p=0.62), with negligible effect size improvements on the Modified Social Support Survey (MSSS) (ES 0.03; 95%CI -0.59 – 0.66; p=0.91).

Analysis of the MSQLI subscales demonstrated that on the MFIS, the largest effect size for improvement was on the subscale for cognitive fatigue (ES 0.57; 95%CI -0.04 – 1.19; p=0.07), followed by psychosocial fatigue (ES 0.49; 95%CI -0.07 – 1.07; p=0.09), and then physical fatigue (ES 0.45; 95%CI -0.08 – 0.99; p=0.10) (Table 6.8). On the MHI, improvements in depression scores had a large effect size (ES 1.35; 95%CI 0.11 – 2.59; p<0.05), as did those for positive affect (ES 0.87; 95%CI -0.27 – 2.00; p=0.13), and anxiety (ES 0.85; 95%CI -0.01 – 1.69; p=0.05) (Table 6.9). Scores for behavioural control had a medium effect size (ES 0.51; 95%CI -0.32 – 1.33; p=0.22) (Table 6.9). Further, cognitive function scores from the PDQ demonstrated improvements on subscales for attention/concentration (ES 0.62; 95%CI 0.05 – 1.19; p<0.05), and prospective memory (ES 0.56; 95%CI -0.01 – 1.14; p=0.05), both of which had medium effect sizes, whilst those on the retrospective memory subscale (ES 0.37; 95%CI -0.16 – 0.91; p=0.17), and the planning/organisation subscale (ES 0.29; 95%CI -0.24 – 0.85; p=0.27) were small (Table 6.10). On the MSSS subscales,

improvements were evident for tangible support with a small effect size (ES 0.26; 95%CI -0.38 – 0.89; p=0.42), whilst those for affectionate support were very small (ES 0.13; 95%CI -0.45 – 0.55; p=0.88), and negligible for positive interactions (ES 0.04; 95%CI -0.48 – 0.55; p=) and emotional support (ES 0.01; 95%CI -0.63 – 0.64; p=0.85) (Table 6.11).

With respect to measures of self-compassion and mindfulness, scores on the Self-Compassion Scale-short form (SCS-sf) (ES 0.78; 95%CI 0.23 – 1.32; p<0.01) and the Mindful-Attention Awareness Scale (MAAS) (ES 0.50; 95%CI -0.08 – 1.09; p=0.09) both improved in the treatment group with a medium effect size (Table 6.12) (Table 6.13). On closer scrutiny of the SCS-sf subscales, improvements noted in the treatment group were largest for common humanity (ES 1.01; 95%CI -0.06 – 1.06; p=0.08) and isolation (ES 0.80; 95%CI 0.26 – 1.40; p<0.01) subscales, with small effect sizes also seen on self-judgement (ES 0.58; 95%CI 0.05 – 1.12; p<0.05), over-identified (ES 0.55; 95%CI 0.02 – 1.07; p<0.05), mindfulness (ES 0.48; 95%CI -0.12 – 1.08; p=0.11), and self-kindness (ES 0.44; 95%CI -0.05 – 0.92; p=0.08) (Table 6.13).

Effect sizes for improved Emotional Lability Questionnaire (ELQ) scores favouring MBSR were negligible at the immediate post-intervention point (ES 0.06; 95%CI -0.42 – 0.51; p=0.85) (Table 6.14)

6.5.4.2.2 Three-month follow-up

At the three-month follow-up point, improvements for MSQLI scores were most evident for the SSS (ES 0.57; 95%CI -0.25 – 1.38; p=0.16) with a medium effect size. Improvements with small effect sizes were also seen on the MFIS (ES 0.33; 95%CI -0.29 – 0.94; p=0.29), the PES (ES 0.32; 95%CI -0.25 – 0.88; p=0.27), the PDQ (ES 0.29; 95%CI -0.41 – 1.00; p=0.41), and the BWCS (ES 0.28; 95%CI -0.27 – 1.60; p=0.31). Improvements for the MHI (ES 0.12; 95%CI -0.52 – 0.81; p=0.66) were very small, and negligible for the BCS (ES 0.05; 95%CI -0.50 – 0.62; p=0.85), and the IVIS (ES 0.04; 95%CI -0.48 – 0.56; p=0.91). Scores for the MSSS showed evidence of deterioration with a small effect size (ES -0.39; 95%CI -0.99 – 0.22; p=0.20) (Table 6.7).

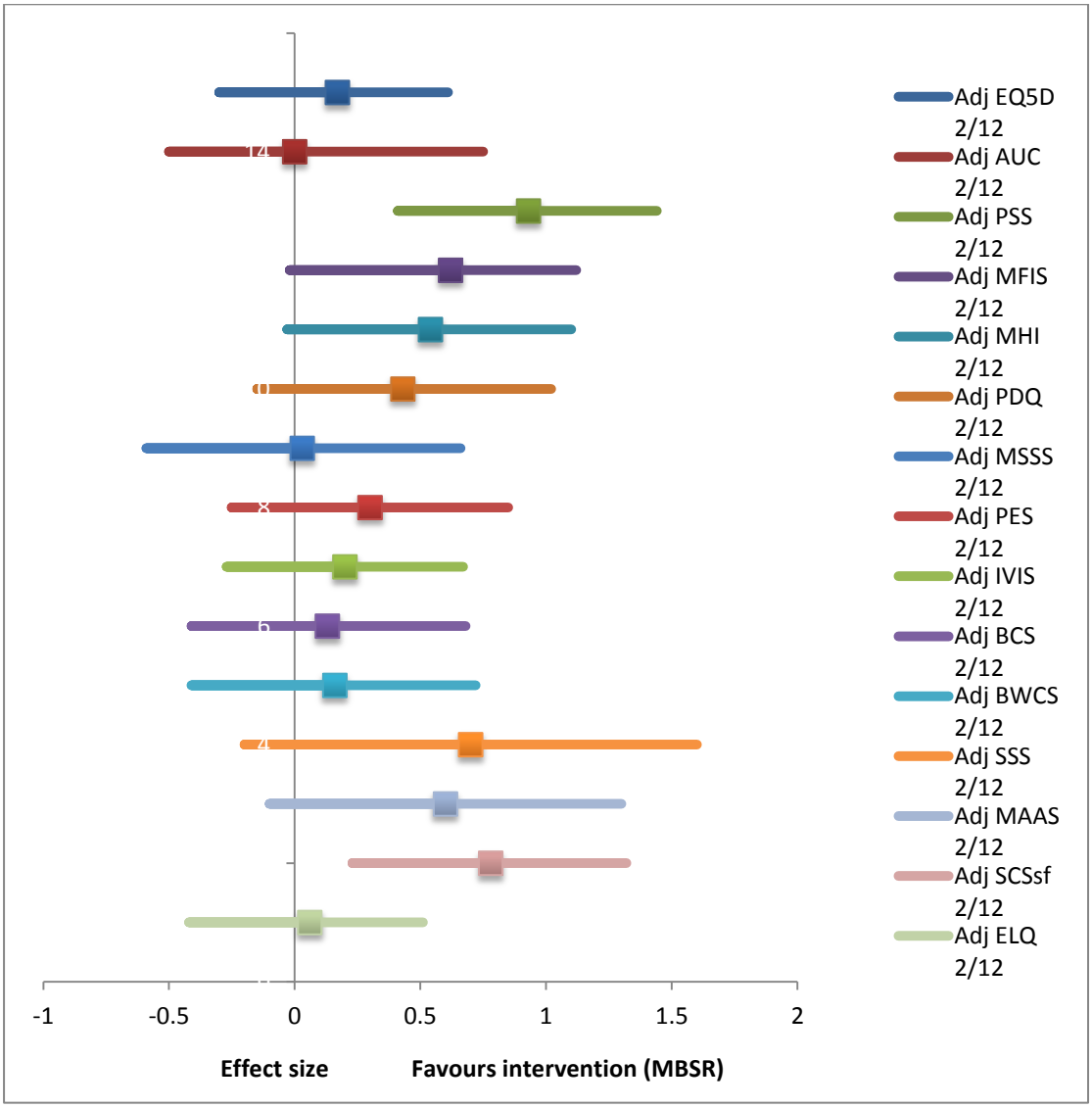
At the three-month follow-up point, analysis of the MSQLI subscales revealed improvements favouring MBSR on the MFIS subscales with small effect sizes for cognitive (ES 0.27; 95%CI -0.34 – 0.88; p=0.38), and psychosocial fatigue (ES 0.23; 95%CI -0.30 – 0.87; p=0.32), and a very small effect size for physical fatigue (ES 0.17; 95%CI -0.33 – 0.67; p=0.49) (Table 6.8). Analysis of the MHI subscales showed persistent reductions in positive affect (ES 0.90; 95%CI -1.88 – 3.89; p=0.54), and anxiety (ES 0.82; 95%CI -0.29 – 1.93; p=0.15), both with large effect sizes. Scores for behavioural control (ES 0.16; 95%CI -1.25 – 0.94; p=0.77) also showed improvement with a small effect size favouring MBSR, but those for depression (ES 0.01; 95%CI -2.60 – 2.59; p=1.00) were negligible (Table 6.9). PDQ subscale scores revealed improvements favouring MBSR with a large effect size for prospective memory (ES 0.81; 95%CI 0.18 – 1.45; p<0.05), and small effect size improvements for retrospective memory (ES 0.35; 95%CI -0.29 – 0.99; p=0.28), planning/organisation (ES 0.31; 95%CI -0.29 – 0.92; p=0.30), and attention (ES 0.23; 95%CI -0.37 – 0.91; p=0.40) (Table 6.10). On the MSSS subscales effect sizes for improved scores favouring MBSR were very small for positive interactions (ES 0.11; 95%CI -0.45 – 0.69; p=0.69), and negligible for affectionate support (ES 0.06; 95%CI -0.53 – 0.64; p=0.85), and tangible support (ES 0.05; 95%CI -0.58 – 0.67; p=0.88). Those for emotional support suggested a deterioration in scores following MBSR, with a small effect (ES -0.22; 95%CI -0.83 – 0.39; p=0.47) (Table 6.11).

At three-month follow-up, improvements with large effect sizes favouring MBSR were evident for mindfulness (MAAS scores) (ES 1.21; 95%CI 0.67 – 1.75; p<0.001) (Table 6.12), and for self-compassion (ES 0.80; 95%CI 0.18 – 1.43; p<0.05) (Table 6.13). Analysis of the SCS-sf subscales revealed improvements favouring MBSR with a large effect size for common-humanity (ES 1.01; 95%CI 0.45 – 1.57; p<0.01), medium effect sizes for self-kindness (ES 0.72; 95%CI 0.13 – 1.22; p<0.05), over-identification (ES 0.68; 95%CI 0.05 – 1.31; p<0.05), and isolation (ES 0.50; 95%CI -0.06 – 1.06; p=0.08), but smaller effect sizes for self-judgement (ES 0.34; 95%CI -0.23 – 0.90; p=0.24), and mindfulness (ES 0.32; 95%CI -0.30 – 0.94; p=0.30) (Table 6.13).

At the three-month follow-up point, effect size for improvements in ELQ scores favouring MBSR were negligible (ES 0.07; 95%CI -0.39 – 0.30; p=0.79) (Table 6.14).

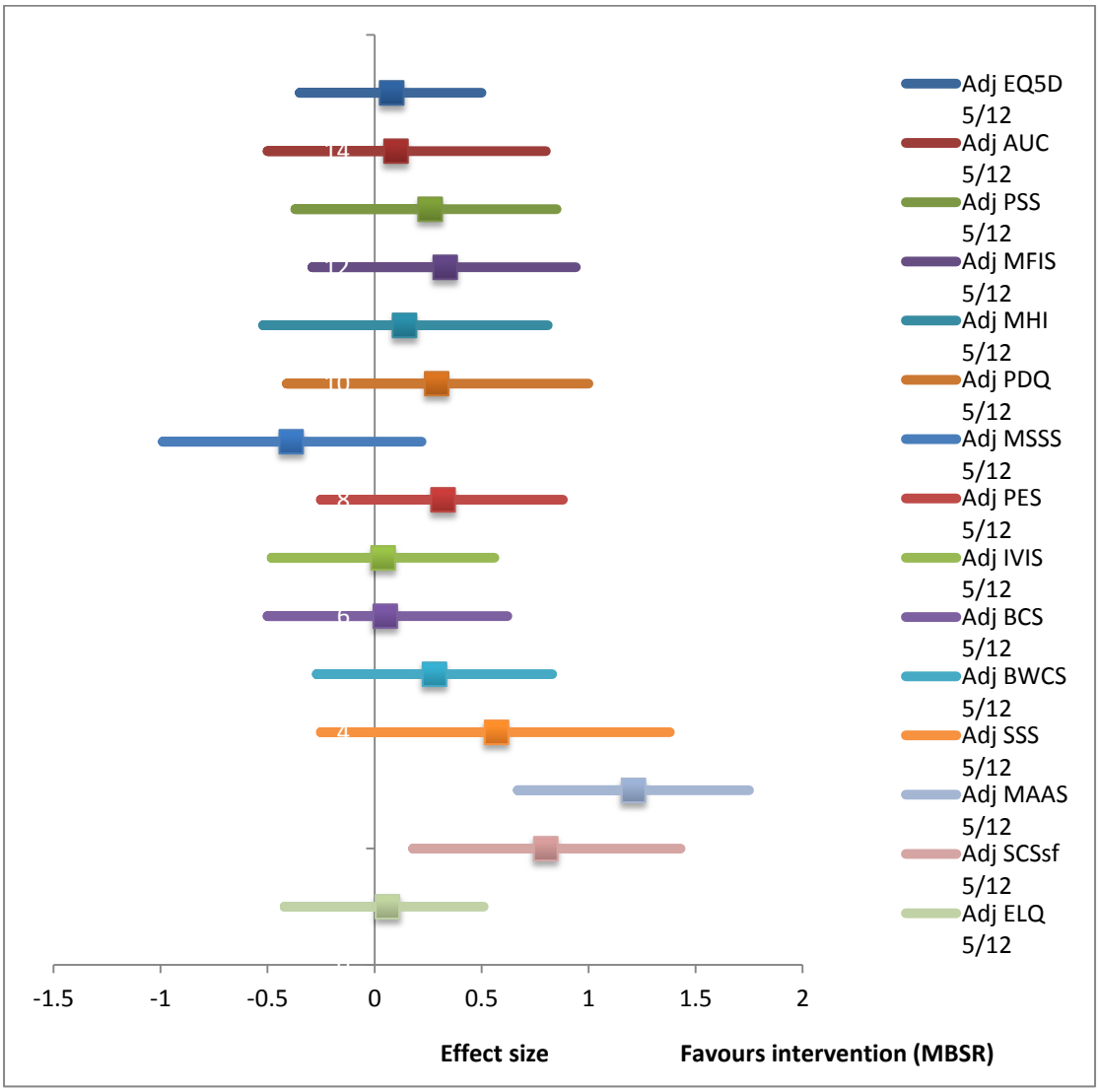
See Figure 6.2 and Figure 6.3 for a graphical summary of overall treatment effects (effect sizes - ESs) for the adjusted models. Also, see Table 6.5 – Table 6.14 for results adjusted for age/sex/SES/previous meditation/yoga experience.

Figure 6.2 Adjusted overall treatment effects with confidence intervals for MBSR at two months (adjusted for age/sex/SES/meditation/yoga)



EQ5D – EuroQol QOL measure adjusted for age/sex/SES/meditation/yoga; AUC – EuroQol Area Under the Curve adjusted for age/sex/SES/meditation/yoga; PSS – Perceived Stress Scale-10 adjusted for age/sex/SES/meditation/yoga; MFIS – Modified Fatigue Impact Scale adjusted for age/sex/SES/meditation/yoga; MHI – Mental Health Inventory adjusted for age/sex/SES/meditation/yoga; PDQ – Perceived Deficits Questionnaire adjusted for age/sex/SES/meditation/yoga; MSSS – Modified Social Support Survey adjusted for age/sex/SES/meditation/yoga; PES – Pain Effects Scale adjusted for age/sex/SES/meditation/yoga; IVIS – Impact of Visual Impairment Scale adjusted for age/sex/SES/meditation/yoga; BCS – Bladder Control Scale adjusted for age/sex/SES/meditation/yoga; BWCS – Bowel Control Scale adjusted for age/sex/SES/meditation/yoga; SSS – Sexual Satisfaction Scale adjusted for age/sex/SES/meditation/yoga; MAAS – Mindful Attention Awareness Scale adjusted for age/sex/SES/meditation/yoga; SCS-sf – Self-Compassion Scale – short form adjusted for age/sex/SES/meditation/yoga; ELQ – Emotional Lability Questionnaire adjusted for age/sex/SES/meditation/yoga

Figure 6.3 Adjusted overall treatment effects with confidence intervals for MBSR at five months (adjusted for age/sex/SES/meditation/yoga)



EQ5D – EuroQol QOL measure adjusted for age/sex/SES/meditation/yoga; AUC – EuroQol Area Under the Curve adjusted for age/sex/SES/meditation/yoga; PSS – Perceived Stress Scale-10 adjusted for age/sex/SES/meditation/yoga; MFIS – Modified Fatigue Impact Scale adjusted for age/sex/SES/meditation/yoga; MHI – Mental Health Inventory adjusted for age/sex/SES/meditation/yoga; PDQ – Perceived Deficits Questionnaire adjusted for age/sex/SES/meditation/yoga; MSSS – Modified Social Support Survey adjusted for age/sex/SES/meditation/yoga; PES – Pain Effects Scale adjusted for age/sex/SES/meditation/yoga; IVIS – Impact of Visual Impairment Scale adjusted for age/sex/SES/meditation/yoga; BCS – Bladder Control Scale adjusted for age/sex/SES/meditation/yoga; BWCS – Bowel Control Scale adjusted for age/sex/SES/meditation/yoga; SSS – Sexual Satisfaction Scale adjusted for age/sex/SES/meditation/yoga; MAAS – Mindful Attention Awareness Scale adjusted for age/sex/SES/meditation/yoga; SCS-sf – Self-Compassion Scale – short form adjusted for age/sex/SES/meditation/yoga; ELQ – Emotional Lability Questionnaire adjusted for age/sex/SES/meditation/yoga

Table 6.5 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for primary stress outcome measure – Perceived Stress Scale-10

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Measure	Time	Intervention	Control	Intervention	Control		
Perceived stress scale - overall	Baseline	21.08 (1.72)	21.96 (1.34)	N/A	N/A	N/A	N/A
	Post	13.50 (7.62)	21.77 (8.01)	-7.50 (-8.00)	-0.32 (-6.27)	-7.34 (-11.44 - -3.23), **p=<0.01**	0.93 (0.41 – 1.44)
	F/u	16.05 (7.94)	18.83 (5.93)	-4.40 (7.16)	-2.87 (4.60)	-1.51 (-5.04 – 2.20), p=0.39	0.26 (-0.37 – 0.85)
Perceived stress scale – negative stressors	Baseline	14.56 (6.09)	14.60 (4.97)	N/A	N/A	N/A	N/A
	Post	9.10 (5.26)	14.23 (5.80)	-5.00 (5.96)	-0.27 (4.76)	-4.75 (-7.81 - -1.69), **p<0.05**	0.82 (0.29 – 1.34)
	F/u	10.15 (6.55)	11.48 (5.30)	-3.75 (5.81)	-3.13 (3.60)	-0.56 (-3.61 – 2.49), p=0.71	0.12 (-0.52 - 0.77)
Perceived stress scale – stress resilience	Baseline	6.79 (2.82)	7.36 (2.72)	N/A	N/A	N/A	N/A
	Post	4.40 (2.58)	7.54 (2.91)	-2.50 (2.48)	0.04 (2.64)	-2.60 (-4.08 - -1.12), **p<0.05**	0.92 (0.40 – 1.45)
	F/u	5.90 (1.92)	7.34 (1.72)	-0.65 (2.28)	0.26 (2.78)	-1.17 (-2.34 - -0.02), p=0.05	0.46 (-0.01 – 0.91)

F/u – Follow up; N/A – Not applicable

Table 6.6 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for primary QOL outcome measures – EQ-5D-5L and Area under the curve analysis

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Measure	Time	Intervention	Control	Intervention	Control		
EQ-5D un-weighted	Baseline	12.20 (3.21)	11.36 (4.20)	N/A	N/A	N/A	N/A
	Post	11.62 (3.22)	11.43 (3.88)	-0.71 (2.00)	-0.13 (2.94)	-0.34 (-1.88 – 1.21), p=0.66	0.13 (-0.48 – 0.74)
	F/u	11.62 (3.57)	11.35 (4.41)	-0.71 (2.01)	0.04 (2.72)	-0.57 (-2.17 – 1.04), p=0.48	0.23 (-0.43 – 0.89)
EQ-5D weighted	Baseline	0.53 (0.23)	0.56 (0.27)	N/A	N/A	N/A	N/A
	Post	0.55 (0.23)	0.59 (0.23)	0.02 (0.18)	0.05 (0.17)	-0.04 (-0.14 – 0.07), p=0.48	0.17 (-0.3 – 0.61)
	F/u	0.54 (0.24)	0.58 (0.28)	0.01 (0.20)	0.02 (0.17)	-0.02 (-0.13 – 0.09), p=0.71	0.08 (-0.35 – 0.50)
EQ-5D – Area under the curve	Baseline	N/A	N/A	N/A	N/A	N/A	N/A
	Post	0.09 (0.04)	0.10 (0.04)	N/A	N/A	0.00 (-0.03 – 0.02), p=0.80	0.00 (-0.50 – 0.75)
	F/u	0.24 (0.09)	0.24 (0.10)	N/A	N/A	-0.01 (-0.08 – 0.05), p=0.71	0.10 (-0.50 – 0.80)
EQ-5D - Mobility	Baseline	2.68 (1.03)	2.44 (1.16)	N/A	N/A	N/A	N/A
	Post	2.67 (1.24)	2.48 (1.12)	-0.14 (0.58)	0.00 (0.85)	-0.05 (-0.53 – 0.44), p=0.85	0.07 (-0.60 – 0.73)
	F/u	2.81 (1.08)	2.43 (1.12)	0.00 (0.55)	0.04 (0.64)	0.07 (-0.31 – 0.46), p=0.70	0.11 (-0.78 – 0.53)
EQ-5D – Self-care	Baseline	1.72 (0.89)	1.64 (0.95)	N/A	N/A	N/A	N/A
	Post	1.81 (0.81)	1.70 (0.93)	0.00 (0.71)	0.00 (0.60)	0.02 (-0.38 – 0.42), p=0.92	0.03 (-0.65 – 0.58)
	F/u	1.76 (0.89)	1.70 (0.88)	0.74 (-0.05)	0.09 (0.73)	-0.07 (-0.51 – 0.38), p=0.77	0.10 (-0.52 – 0.70)

EQ-5D – Usual activities	Baseline	2.64 (0.91)	2.44 (1.19)	N/A	N/A	N/A	N/A
	Post	2.57 (0.87)	2.48 (1.12)	0.00 (0.89)	0.00 (1.04)	0.01 (-0.55 – 0.57), p=0.97	0.01 (-0.59 – 0.57)
	F/u	2.52 (1.08)	2.57 (1.20)	-0.05 (0.86)	0.13 (0.97)	-0.11 (-0.67 – 0.46), p=0.69	0.12 (-0.51 – 0.74)
EQ-5D – Pain/ discomfort	Baseline	2.72 (1.17)	2.60 (1.15)	N/A	N/A	N/A	N/A
	Post	2.62 (0.97)	2.61 (1.03)	-0.10 (0.44)	-0.04 (0.77)	0.03 (-0.32 – 0.39), p=0.86	0.05 (-0.63 – 0.52)
	F/u	2.57 (1.03)	2.52 (1.16)	-0.14 (0.57)	-0.09 (0.73)	-0.04 (-0.45 – 0.37), p=0.85	0.06 (-0.57 – 0.69)
EQ-5D – Anxiety/ depression	Baseline	2.44 (0.82)	2.24 (0.83)	N/A	N/A	N/A	N/A
	Post	1.95 (0.67)	2.17 (0.89)	-0.47 (0.68)	-0.09 (0.73)	-0.30 (-0.71 – 0.12), p=0.16	0.41 (-0.16 – 0.97)
	F/u	1.95 (0.97)	2.13 (0.97)	-0.48 (0.93)	-0.13 (0.69)	-0.21 (-0.74 – 0.31), p=0.42	0.26 (-0.38 – 0.90)

F/u – Follow up; N/A – Not applicable

Table 6.7 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for the Multiple Sclerosis Quality of Life Inventory

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Measure	Time	Intervention	Control	Intervention	Control		
Modified fatigue impact scale - MFIS	Baseline	53.21 (18.68)	54.26 (16.77)	N/A	N/A	N/A	N/A
	Post	38.47 (19.84)	49.91 (17.19)	-13.33 (14.56)	-4.18 (10.87)	-8.32 (-16.87 – 0.24), p=0.06	0.62 (-0.02 – 1.12)
	F/u	42.95 (18.58)	50.00 (15.54)	-9.5 (14.58)	-3.91 (11.15)	-4.24 (-12.21 – 3.75), p=0.29	0.33 (-0.29 – 0.94)
Mental health inventory - MHI	Baseline	68.92 (17.48)	67.45 (16.87)	N/A	N/A	N/A	N/A
	Post	83.52 (14.18)	74.22 (16.53)	13.43 (13.65)	6.10 (13.00)	7.34 (-0.36 – 15.05), p=0.06	0.54 (-0.03 – 1.10)
	F/u	78.29 (19.60)	73.41 (17.08)	8.19 (18.44)	6.25 (8.73)	2.08 (-7.46 – 11.62), p=0.66	0.14 (- 0.52 – 0.81)
Perceived deficits scale - PDQ	Baseline	38.48 (16.24)	39.04 (14.36)	N/A	N/A	N/A	N/A
	Post	29.05 (12.31)	34.32 (14.81)	-9.00 (12.98)	-4.10 (8.77)	-4.77 (-11.17 – 1.64), p=0.14	0.43 (-0.15 – 1.02)
	F/u	33.18 (16.94)	35.23 (14.65)	-5.47 (7.16)	-2.29 (7.71)	-2.21 (-7.54 – 3.13), p=0.41	0.29 (-0.41 – 1.00)
Modified social support survey - MSSS	Baseline	44.61 (25.05)	43.12 (20.74)	N/A	N/A	N/A	N/A
	Post	45.60 (26.93)	41.45 (17.01)	0.99 (10.62)	-1.67 (15.69)	0.47 (-8.05 – 8.99), p=0.91	0.03 (-0.59 – 0.66)
	F/u	44.00 (25.40)	45.27 (21.36)	0.61 (8.99)	2.15 (16.98)	-5.60 (-14.34 – 3.15), p=0.20	-0.39 (-0.99 – 0.22)
Pain effects scale - PES	Baseline	17.76 (5.75)	18.17 (6.04)	N/A	N/A	N/A	N/A
	Post	14.29 (4.71)	17.00 (5.65)	-3.47 (4.13)	-1.17 (5.48)	-1.90 (-4.41 – 0.61), p=0.13	0.44 (-0.14 – 1.01)
	F/u	14.48 (5.73)	17.22 (5.69)	-3.28 (4.82)	-0.95 (4.70)	-1.56 (-4.35 – 1.23), p=0.27	0.32 (-0.25 – 0.88)

Impact of visual impairment scale - IVIS	Baseline	7.08 (3.29)	7.54 (3.64)	N/A	N/A	N/A	N/A
	Post	6.55 (2.52)	7.37 (3.12)	-0.53 (3.36)	-0.17 (3.16)	-0.80 (-2.21 – 0.61), p=0.26	0.30 (-0.23 – 0.82)
	F/u	6.90 (2.77)	7.47 (3.30)	-0.18 (3.14)	-0.07 (3.23)	0.11 (-1.46 – 1.25), p=0.91	0.04 (-0.48 – 0.56)
Bladder control scale - BCS	Baseline	9.71 (6.15)	9.33 (5.82)	N/A	N/A	N/A	N/A
	Post	7.86 (4.79)	7.61 (4.67)	-1.85 (3.94)	-1.72 (3.72)	0.51 (-1.56 – 2.58), p=0.62	0.13 (-0.41 – 0.68)
	F/u	7.90 (4.75)	8.13 (5.21)	-1.81 (4.50)	-1.20 (3.15)	-0.20 (-2.33 – 1.90), p=0.85	0.05 (-0.50 – 0.62)
Bowel control scale - BWCS	Baseline	11.87 (6.19)	9.04 (6.43)	N/A	N/A	N/A	N/A
	Post	9.80 (5.25)	8.09 (5.15)	-2.07 (2.97)	-0.95 (6.08)	0.77 (-2.02 – 3.56), p=0.58	0.16 (-0.41 – 0.72)
	F/u	10.05 (5.58)	8.09 (4.44)	-1.82 (5.24)	-0.95 (4.96)	1.40 (-1.37 – 4.17), p=0.31	0.28 (-0.27 – 0.83)
Sexual satisfaction scale - SSS	Baseline	13.00 (6.50)	13.84 (6.87)	N/A	N/A	N/A	N/A
	Post	8.80 (3.88)	14.89 (6.50)	4.20 (4.34)	-1.05 (3.56)	-2.68 (-6.11 – 0.75), p=0.12	0.70 (-0.20 – 1.60)
	F/u	8.90 (4.43)	14.69 (7.00)	-4.10 (2.50)	-0.85 (4.85)	-2.46 (-6.01 – 1.08), p=0.16	0.57 (-0.25 – 1.38)

F/u – Follow up; N/A – Not applicable

Table 6.8 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for Modified Fatigue Impact Scale sub-scales

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Measure	Time	Intervention	Control	Intervention	Control		
Modified fatigue impact scale - overall	Baseline	53.21 (18.68)	54.26 (16.77)	N/A	N/A	N/A	N/A
	Post	38.47 (19.84)	49.91 (17.19)	-13.33 (14.56)	-4.18 (10.87)	-8.32 (-16.87 – 0.24), p=0.06	0.62 (-0.02 – 1.12)
	F/u	42.95 (18.58)	50.00 (15.54)	-9.5 (14.58)	-3.91 (11.15)	-4.24 (-12.21 – 3.75), p=0.29	0.33 (-0.29 – 0.94)
Modified fatigue impact scale - cognitive	Baseline	24.04 (8.89)	23.75 (7.18)	N/A	N/A	N/A	N/A
	Post	16.90 (8.49)	22.04 (8.55)	-6.55 (7.03)	-1.77 (5.87)	-3.91 (-8.09 – 0.27), p=0.07	0.57 (-0.04 - 1.19)
	F/u	17.80 (9.51)	21.17 (7.37)	-5.25 (7.13)	-2.36 (5.54)	-1.73 (-5.67 – 2.19), p=0.38	0.27 (-0.34 - 0.88)
Modified fatigue impact scale - physical	Baseline	24.68 (9.30)	26.92 (11.22)	N/A	N/A	N/A	N/A
	Post	18.32 (10.08)	23.96 (8.23)	-6.16 (6.94)	-3.00 (7.64)	-3.36 (-7.36 – 0.62), p=0.10	0.45 (-0.08 – 0.99)
	F/u	21.19 (8.05)	24.13 (8.08)	-3.48 (7.53)	-2.56 (8.41)	-1.38 (-5.35 – 2.60), p=0.49	0.17 (-0.33 – 0.67)
Modified fatigue impact scale - psychosocial	Baseline	4.72 (2.42)	5.08 (2.30)	N/A	N/A	N/A	N/A
	Post	3.45 (2.30)	4.54 (2.04)	-1.40 (1.79)	-0.54 (1.47)	-0.82 (-1.77 – 0.12), p=0.09	0.49 (-0.07 - 1.07)
	F/u	3.95 (2.40)	4.70 (2.01)	-0.90 (1.97)	-0.39 (1.47)	-0.50 (-1.51 – 0.51), p=0.32	0.23 (-0.30 – 0.87)

Table 6.9 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for Mental Health Inventory sub-scales

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Measure	Time	Intervention	Control	Intervention	Control		
Mental health inventory - overall	Baseline	68.92 (17.48)	67.45 (16.87)	N/A	N/A	N/A	N/A
	Post	83.52 (14.18)	74.22 (16.53)	13.43 (13.65)	6.10 (13.00)	7.34 (-0.36 – 15.05), p=0.06	0.54 (-0.03 – 1.10)
	F/u	78.29 (19.60)	73.41 (17.08)	8.19 (18.44)	6.25 (8.73)	2.08 (-7.46 – 11.62), p=0.66	0.14 (- 0.52 – 0.81)
Mental health inventory - anxiety	Baseline	51.84 (23.79)	51.84 (17.45)	N/A	N/A	N/A	N/A
	Post	72.76 (17.23)	59.65 (24.77)	18.86 (20.20)	8.17 (17.87)	11.15 (-0.04 – 22.34), p=0.05	0.85 (-0.01 – 1.69)
	F/u	67.43 (23.91)	57.56 (22.84)	13.52 (21.45)	6.26 (13.20)	7.96 (-2.88 – 18.81), p=0.15	0.82 (-0.29 – 1.93)
Mental health inventory - depression	Baseline	64.60 (23.14)	60.42 (24.04)	N/A	N/A	N/A	N/A
	Post	78.57 (17.19)	64.38 (20.18)	11.90 (17.43)	3.91 (19.24)	10.41 (0.84 – 20.00), **p<0.05**	1.35 (0.11 – 2.59)
	F/u	70.71 (23.04)	65.68 (22.43)	4.04 (21.72)	5.00 (14.83)	-0.03 (-11.75 – 11.70), p=1.00	0.01 (-2.60 – 2.59)
Mental health inventory – behavior control	Baseline	62.80 (25.17)	57.29 (21.97)	N/A	N/A	N/A	N/A
	Post	78.33 (17.56)	68.33 (22.44)	14.29 (21.29)	9.57 (14.30)	6.01 (-3.80 – 15.81), p=0.22	0.51(-0.32 – 1.33)
	F/u	74.29 (23.84)	71.08 (20.34)	10.24 (24.92)	11.81 (13.68)	-1.73 (-13.85 – 10.39), p=0.77	0.16 (-1.25 – 0.94)
Mental health inventory – positive affect	Baseline	46.60 (21.10)	48.00 (23.23)	N/A	N/A	N/A	N/A
	Post	62.62 (17.86)	53.12 (20.68)	14.29 (18.05)	4.37 (20.13)	7.80 (-2.39 – 18.00), p=0.13	0.87 (-0.27 – 2.00)
	F/u	55.24 (25.37)	51.52 (21.71)	6.90 (25.22)	1.96 (16.57)	3.91 (-8.92 – 16.75), p=0.54	0.90 (-1.88 – 3.89)

F/u – Follow up; N/A – Not applicable

Table 6.10 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for Perceived Deficits Questionnaire sub-scales

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Measure	Time	Intervention	Control	Intervention	Control		
Perceived deficits questionnaire - overall	Baseline	38.48 (16.24)	39.04 (14.36)	N/A	N/A	N/A	N/A
	Post	29.05 (12.31)	34.32 (14.81)	-9.00 (12.98)	-4.10 (8.77)	-4.77 (-11.17 – 1.64), p=0.14	0.43 (-0.15 – 1.02)
	F/u	33.18 (16.94)	35.23 (14.65)	-5.47 (7.16)	-2.29 (7.71)	-2.21 (-7.54 – 3.13), p=0.41	0.29 (-0.41 – 1.00)
Perceived deficits questionnaire - attention	Baseline	11.74 (4.18)	11.08 (3.82)	N/A	N/A	N/A	N/A
	Post	8.75 (3.08)	10.22 (4.25)	-2.72 (2.89)	-1.05 (2.05)	-1.59 (-3.05 - -0.12), **p<0.05**	0.62 (0.05 – 1.19)
	F/u	9.00 (4.61)	9.91 (4.05)	-2.11 (2.72)	-1.05 (2.46)	-0.70 (-2.37 – 0.97), p=0.40	0.23 (-0.37 – 0.91)
Perceived deficits questionnaire - retrospective memory	Baseline	9.16 (4.5)	9.16 (4.10)	N/A	N/A	N/A	N/A
	Post	7.30 (3.66)	8.67 (4.12)	-1.65 (3.78)	-0.58 (2.84)	-1.24 (-3.02 – 0.53), p=0.17	0.37 (-0.16 – 0.91)
	F/u	7.57 (4.56)	8.68 (4.02)	-1.33 (2.99)	-0.18 (2.63)	-0.99 (-2.81 – 0.83), p=0.28	0.35 (-0.29 – 0.99)
Perceived deficits questionnaire – prospective memory	Baseline	7.42 (3.81)	7.28 (3.59)	N/A	N/A	N/A	N/A
	Post	5.75 (2.90)	7.25 (3.77)	-1.58 (3.29)	-0.05 (2.33)	-1.61 (-3.25 – 0.03), p=0.05	0.56 (-0.01 – 1.14)
	F/u	6.00 (4.02)	7.05 (4.05)	-2.00 (2.40)	-0.09 (1.87)	-1.88 (-3.34 - -0.41), **p<0.05**	0.81 (0.18 – 1.45)
Perceived deficits questionnaire – planning/ organisation	Baseline	9.80 (5.25)	10.48 (3.75)	N/A	N/A	N/A	N/A
	Post	7.15 (3.99)	8.87 (3.67)	-2.15 (4.23)	-1.57 (3.64)	-1.15 (-3.21 – 0.92), p=0.27	0.29 (-0.24 – 0.85)
	F/u	7.90 (4.89)	9.59 (3.80)	-1.70 (3.18)	-0.64 (2.52)	-0.90 (-2.64 – 0.84), p=0.30	0.31 (-0.29 – 0.92)

Table 6.11 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for Modified Social Support Survey sub-scales

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Measure	Time	Intervention	Control	Intervention	Control		
Modified social support survey - overall	Baseline	44.61 (25.05)	43.12 (20.74)	N/A	N/A	N/A	N/A
	Post	45.60 (26.93)	41.45 (17.01)	0.99 (10.62)	-1.67 (15.69)	0.47 (-8.05 – 8.99), p=0.91	0.03 (-0.59 – 0.66)
	F/u	44.00 (25.40)	45.27 (21.36)	0.61 (8.99)	2.15 (16.98)	-5.60 (-14.34 – 3.15), p=0.20	-0.39 (-0.99 – 0.22)
Modified social support survey - tangible	Baseline	58.85 (35.69)	57.50 (33.95)	N/A	N/A	N/A	N/A
	Post	64.88 (39.99)	59.78 (32.36)	4.68 (21.73)	3.53 (20.11)	5.30 (-7.86 – 18.46), p=0.42	0.26 (-0.38 – 0.89)
	F/u	62.20 (37.42)	59.23 (35.55)	0.63 (19.12)	2.98 (26.77)	1.07 (-13.51 – 15.56), p=0.88	0.05 (-0.58 – 0.67)
Modified social support survey - emotional	Baseline	63.88 (34.07)	62.13 (29.61)	N/A	N/A	N/A	N/A
	Post	64.38 (38.06)	63.32 (29.25)	-4.84 (22.06)	0.27 (27.06)	0.29 (-15.53 – 16.00), p=0.98	0.01 (-0.63 – 0.64)
	F/u	60.27 (34.73)	63.32 (28.90)	-6.84 (22.91)	0.82 (23.50)	-5.12 (-19.27 – 9.04), p=0.47	-0.22 (-0.83 – 0.39)
Modified social support survey - affection	Baseline	53.67 (36.65)	53.00 (33.50)	N/A	N/A	N/A	N/A
	Post	57.54 (41.07)	53.82 (28.34)	1.59 (28.21)	24.08 (0.00)	3.43 (-11.55 – 18.41), p=0.65	0.13 (-0.45 – 0.71)
	F/u	58.73 (38.23)	60.98 (36.50)	2.78 (32.10)	7.19 (32.76)	-1.83 (-20.68 – 17.01), p=0.85	0.06 (-0.53 – 0.64)
Modified social support survey – positive interactions	Baseline	69.10 (38.58)	64.00 (32.52)	N/A	N/A	N/A	N/A
	Post	61.11 (35.19)	55.80 (23.89)	-13.33 (20.30)	-6.16 (24.26)	0.85 (-10.74 – 12.44), p=0.88	0.04 (-0.48 – 0.55)
	F/u	66.67 (37.46)	64.13 (34.85)	-10.96 (19.26)	-0.36 (29.46)	-2.85 (-17.37 – 11.66), p=0.69	0.11 (-0.45 - 0.69)

F/u – Follow up; N/A – Not applicable

Table 6.12 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for the Mindful Attention Awareness Scale

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Measure	Time	Intervention	Control	Intervention	Control		
Mindful attention awareness scale - MAAS	Baseline	3.47 (1.15)	3.32 (0.72)	N/A	N/A	N/A	N/A
	Post	4.52 (0.65)	3.88 (0.94)	0.85 (0.67)	-0.53 (0.77)	0.44 (-0.07 – 0.96), p=0.09	0.50 (-0.08 – 1.09)
	F/u	4.42 (0.51)	3.45 (0.84)	1.04 (0.78)	0.11 (0.50)	0.96 (0.54 – 1.39), **p<0.001**	1.13 (0.63 – 1.64)

F/u – Follow up; N/A – Not applicable

Table 6.13 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for the Self-Compassion Scale-short form

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Measure	Time	Intervention	Control	Intervention	Control		
Self-compassion scale – short form - overall	Baseline	2.63 (0.85)	2.71 (0.73)	N/A	N/A	N/A	N/A
	Post	3.56 (0.82)	2.82 (0.90)	0.92 (0.85)	0.11 (0.68)	0.68 (0.22 – 1.14), **p<0.01**	0.80 (0.26 – 1.34)
	F/u	3.44 (0.98)	2.68 (0.80)	0.77 (0.92)	0.03 (0.61)	0.70 (0.17 – 1.23) **p<0.05**	0.83 (0.20 – 1.46)
Self-compassion scale – short form – self kindness	Baseline	5.00 (2.19)	5.28 (2.21)	N/A	N/A	N/A	N/A
	Post	6.90 (1.84)	5.46 (2.30)	1.95 (2.06)	0.17 (2.55)	1.08 (-0.12 – 2.27), p=0.08	0.44 (-0.05 – 0.92)
	F/u	6.47 (2.48)	4.70 (2.03)	1.44 (2.66)	-0.50 (2.24)	1.78 (0.36 – 3.19), **p<0.05**	0.72 (0.13 – 1.22)
Self-compassion scale – short form – self judging	Baseline	4.38 (2.22)	4.96 (2.17)	N/A	N/A	N/A	N/A
	Post	6.90 (2.10)	5.50 (2.30)	2.35 (2.66)	0.58 (2.24)	1.50 (0.12 – 2.88), **p<0.05**	0.58 (0.05 – 1.12)
	F/u	6.58 (2.59)	5.75 (1.65)	2.00 (2.74)	0.85 (2.23)	0.85 (-0.58 – 2.29), p=0.24	0.34 (-0.23 - 90)
Self-compassion scale – short form – common humanity	Baseline	5.79 (2.20)	5.68 (2.25)	N/A	N/A	N/A	N/A
	Post	7.09 (2.07)	5.75 (2.25)	1.45 (2.61)	0.83 (2.26)	1.15 (-0.16-2.46), p=0.08	0.46 (-0.06 – 0.99)
	F/u	7.67 (2.06)	4.95 (2.33)	1.76 (2.41)	0.65 (1.87)	2.46 (1.10 – 3.83), **p<0.01**	1.01 (0.45 – 1.57)
Self-compassion scale – short form - isolation	Baseline	4.92 (2.50)	5.20 (2.08)	N/A	N/A	N/A	N/A
	Post	7.24 (2.53)	5.37 (2.58)	2.20 (2.37)	0.21 (2.17)	2.03 (0.63 – 3.44), **p<0.01**	0.80 (0.26 – 1.40)
	F/u	6.63 (2.24)	5.45 (2.21)	1.44 (2.71)	0.50 (2.59)	1.33 (-0.16 – 2.82), p=0.08	0.50 (-0.06 – 1.06)

Self-compassion scale – short form - mindfulness	Baseline	7.00 (2.06)	6.68 (1.95)	N/A	N/A	N/A	N/A
	Post	7.81 (2.20)	6.33 (2.23)	0.75 (1.92)	0.42 (1.98)	0.97 (-0.24 – 2.18), p=0.11	0.48 (-0.12 – 1.08)
	F/u	7.74 (2.16)	6.20 (2.44)	0.28 (2.40)	-0.55 (2.16)	0.73 (-0.69 – 2.14), p=0.30	0.32 (-0.30 – 0.94)
Self-compassion scale – short form – over-identification	Baseline	4.50 (2.52)	4.76 (2.01)	N/A	N/A	N/A	N/A
	Post	6.76 (2.23)	5.38 (2.28)	2.30 (2.08)	0.75 (1.78)	1.12 (0.04 – 2.19), **p<0.05**	0.55 (0.02 – 1.07)
	F/u	6.74 (2.58)	5.10 (2.13)	2.06 (2.21)	0.70 (1.63)	1.37 (0.10 – 2.64), **p<0.05**	0.68 (0.05 – 1.31)

F/u – Follow up; N/A – Not applicable

Table 6.14 Adjusted scores (Age, sex, deprivation, previous meditation/yoga experience) for the Emotional Lability Questionnaire

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size
Measure	Time	Intervention	Control	Intervention	Control		
ELQ	Baseline	15.19 (14.18)	15.46 (11.33)	N/A	N/A	N/A	N/A
	Post	9.56 (10.15)	9.14 (9.56)	-5.63 (9.67)	-6.32 (8.21)	-0.55 (-6.47 – 5.36), p=0.85	0.06 (-0.42 – 0.51)
	F/u	8.72 (11.31)	11.00 (8.29)	-6.47 (13.58)	-4.46 (8.01)	-0.79 (-6.76 – 5.18), p=0.79	0.07 (-0.39 – 0.30)

F/u – Follow up; N/A – Not applicable.

Discussion

6.5.5 Summary of key findings

This study assessed the key feasibility outcomes from a RCT delivering MBSR to people with MS. The recruitment target of 50 participants was met within the pre-defined three-month period. Study retention rates were excellent (88% or above), and missing values generally low. In terms of primary patient outcomes, perceived stress scores improved at post-intervention for those receiving MBSR with a large effect size, although effect sizes at three-month follow-up were small. Improvements in QOL scores were very small at both the immediate post-intervention and three-month follow-up points. Secondary patient report outcomes showed improvements with large effect sizes immediately post-intervention in scores for depression, positive affect, anxiety, and self-compassion. At three-month follow-up, improvements with a persisting large effect size were evident for positive affect, anxiety, and self-compassion, with large effect size improvements also being evident for mindfulness and prospective memory.

6.5.6 Comparison with the existing literature and emergent recommendations

6.5.6.1 Feasibility findings

Previous studies of MBIs in MS have been diverse. A high quality RCT from Switzerland (n=150) [177] assessed standard MBSR in less disabled people with MS (mean EDSS 3.0; SD 1.0), in a university hospital setting. Recruitment methods were not well described by Grossman et al. [177], other than that over a six-month period a total of 164 patients with MS self-referred to the study in response to adverts placed in the hospital. The refusal rate was lower than in the current study (24%), at 9%, which may be down to the opt-in strategy Grossman et al. [177] employed, or that the current study recruitment strategy had a wider reach. Attendance in the Grossman et al. [177] study was very good (92%). Grossman et al. [250] did not report on the

extent of missing values in their study. Class sizes appear to have been smaller with 10-15 participants per group, versus 25 in the current study, which may be a factor in the higher attendance rates. Average home practice times in Grossman et al. [177] of 29.2 minutes/day was comparable to findings in the present study (32.5 minutes/day). MBSR teachers in Grossman et al. [177] were experienced (>9 years), versus 7.5 years in the current study. Outcome measure completion in Grossman et al. [177] was 91% at six-month follow-up, compared with 88% at three-month follow-up in this current study.

In England, in a RCT using a Skype-delivered MBCT intervention with shortened mediation exercises of 10-20 minutes, Bogosian et al. [305] recruited participants with progressive MS, with the mean (SD) EDSS being 6.5 (1.5), indicating high levels of disability – in this current study the mean (SD) EDSS was 4.4 (1.8). Participants were only eligible if demonstrating baseline levels of distress, as measured by the General Health Questionnaire (GHQ). Bogosian et al. [305] removed mindful-movement from the course, based on limited stakeholder input. Bogosian et al. [305] reported an attrition rate of 20%, but reasons accounting for this finding were vague. Bogosian et al. [305] did not report on levels of missing values. From sending out 165 information packs, 115 people responded, 93 were screened, and 40 were deemed eligible and included. Thus, from the figures provided by Bogosian et al. [305], response rate to invitation was 70% (115/165), refusal rate was 67% (77/115), and consent rate was 43% (40/93). Attendance at the shortened one-hour long MBCT classes in Bogosian et al. [305] was good (95%), compared with 60% in this current study, however, no figures were available for home practice times. In Bogosian et al. [305], the MBCT classes were taught by the study's primary author (A. Bogosian), potentially introducing an important source of bias. A Bogosian had received mindfulness training and had run supervised pilot sessions prior to the MBCT course taking place, but no further details were available with respect to years of experience as a mindfulness teacher.

6.5.6.2 Patient report outcome findings

Improvements in perceived stress in those receiving MBSR were large in this study at the intermediate time point, whilst those for QOL were very small. No prior MBI

study in people with MS has measured the impact of mindfulness training on perceived stress using the PSS, although Bogosian et al. [305] reported a significant improvement in distress measured via the GHQ post-MBCT (ES 0.67; $p<0.05$), and three months later (ES 0.97; $p<0.05$). In addition, Kolahkaj and Zargar [306] described significantly improved stress scores on the stress subscale of the Depression, Anxiety, and Stress Scale-21 (DASS-21) post-MBSR (ES 1.91; $p<0.001$) and at one-month follow-up (ES 1.98; $p<0.001$) amongst Iranian women with MS. However, findings from this latter study should be interpreted with caution due to the low quality of methods and reporting (see Appendix D).

In this current study, it is not clear why such small differences were found in QOL scores between the groups, but it is notable that the largest effect size for improvement was on the anxiety/depression subscale, and that higher levels of disability have recently been shown to exert an even greater negative impact on QOL than depression in people with MS [73]. This may partially explain why neither Bogosian et al. [305], nor this current study demonstrated improved QOL, where both were using the generic EQ-5D-5L, whilst those studies with lower mean EDSS scores (3.0) [177, 304] did find improved scores for QOL, using a mix of generic and/or MS-specific scales [177] (generic: PQOLC - Profile of Health-Related Quality of Life in Chronic Disorders: ES 0.86; $p<0.05$; and MS-specific: HAQUAMS - Hamburg Quality of Life Questionnaire in Multiple Sclerosis: ES 0.43; $p<0.05$); or generic alone [304] (QLS - Quality of Life Satisfaction questionnaire: ES 1.03; $p<0.05$).

With respect to secondary patient outcomes in the current study, improvements with a large effect size were evident at the intermediate time point for scores for depression, positive affect, anxiety, and self-compassion, whilst at follow-up large effect size improvements were evident for mindfulness, positive affect, anxiety, self-compassion, and prospective memory. In other MBI studies among people with MS that reported on mental health outcomes, Grossman et al. [177] described improvements in scores for depression at post-intervention (ES 0.65; $p<0.001$), which were smaller at six-month follow-up (ES 0.36; $p<0.05$), and anxiety post-intervention (ES 0.39; $p<0.001$), which were sustained at six-month follow-up (ES 0.36; $p<0.05$). Grossman et al. [177] also carried out sub-group analyses, selecting only those participants with pre-intervention impairment, where outcome measures indicated clinically significant

anxiety and depression. In both conditions, these ancillary analyses increased effect sizes to large. Bogosian et al. [305] reported medium-large beneficial effects on anxiety (ES 0.86; p<0.05); and depression (ES 0.65; p<0.05) post-MBCT, and three months later (ES 0.53; p<0.05). Kohlakaj and Zargar [306] reported significant improvements in depression at post-MBSR (ES 2.00; p<0.001), and at one-month follow-up (ES 2.16; p<0.001); as well as anxiety post-MBSR (ES 2.62; p<0.001) and at one-month follow-up (ES 2.23; p<0.001). For a summary of effect sizes for mental health outcomes reported in studies of standardised MBIs in people with MS, see Table 6.15.

Table 6.15 Mental health outcomes in standardised MBIs for people with MS

Study (n)	Intervention	Mental health outcome	Post-intervention effect size (p)	Follow-up effect size* (p)/ timing
Current study (50)	MBSR			*3-months post MBSR*
		PSS	0.93 (<0.01)	0.26 (p=0.39)
		MHA	0.85 (0.05)	0.82 (0.15)
		MHD	1.35(<0.05)	0.01 (1.00)
Kolhakaj and Zargar [306] (40)	MBSR			*1-month post MBSR*
		DASS-A	2.62 (<0.001) $^{\phi}$	2.23 (<0.001)
		DASS-D	2.00 (<0.001) $^{\phi}$	2.16 (<0.001)
		DASS-S	1.72 (<0.001) $^{\phi}$	1.75(<0.001)
Bogosian et al. [305] (40)	MBCT			*3-months post MBCT*
		GHQ	0.67 (<0.05)	0.97 (<0.05)
		HADS-A	0.40 (<0.05)	0.99 (<0.05)
		HADS-D	0.65 (<0.05)	0.65 (<0.05)
Grossman et al. [177] $^{\Upsilon}$ (150)	MBSR			*6-months post MBSR*
		STAI	0.39 (p<0.001)	0.36 (p<0.05)
		CES-D	0.65 (p<0.0001)	0.36 (<0.05)

1. Perceived Stress Scale; 2. MHD = Mental Health Inventory (MHI) – Depression; 3. MHA = MHI – Anxiety; 4. DASS-A Depression, Anxiety, and Stress score (DASS) – Anxiety; 5. DAAS-D = DASS – Depression; 6. DASS-S = DASS – Stress; 7. GHQ = General Health Questionnaire; 8. HADS-A = Hospital Anxiety and Depression Scale (HADS) – anxiety; 9. HADS – D = HADS – Depression; 10. CES-D = Centre for Epidemiologic Studies scale – Depression; 11. STAI = Spielberger Trait Anxiety Inventory.

*All effect sizes at three-months, apart from Kolhakaj and Zargar [306] (one-month); Grossman et al. [177] (six months)

$^{\Upsilon}$ Effect sizes reported only for full group analysis in this case.

$^{\phi}$ Effect size not reported in publication, but calculated from mean between group treatment effects ÷standard deviations

Aside from this current study, only Grossman et al. [177] reported measuring cognitive function, at baseline and at six-month follow-up. However, the authors described the measure as a screening test, and no results were presented in their publication, or additional files. Direct comparison is thus impossible, but a systematic review [280] on the effects of MBIs on cognitive abilities amongst healthy and clinical samples reported that mindfulness training was associated with improvements in selective and executive attention, and working memory. However, most of the positive findings in this review related to healthy subjects, and beneficial effects in clinical groups were only recorded in subjects with MDD undertaking MBCT, where positive effects were limited to autobiographical memory tests alone [280].

In the case of mindfulness and self-compassion, no previous MBI studies in people with MS have measured mindfulness, so a direct comparison is not possible. However, in the case of self-compassion, Bogosian et al. [313] recently reported small, non-significant improvements in self-compassion in people with progressive MS completing a Skype-delivered MBCT programme, with effect sizes increasing from immediately post-intervention (ES 0.21; p=0.42) to three-month follow-up (ES 0.45; p=0.35). Self-compassion was also included in a mediation analysis by Bogosian et al. [313], assessing the potential role self-compassion might have in improvements noted in GHQ scores for psychological distress. Self-compassion contributed 14.7% to improvements immediately post-MBCT, and 11.4% at three-month follow-up. In cross-sectional studies, greater mindfulness has been associated with improved wellbeing and QOL, diminished distress, and improved coping in people with MS [200], besides enhanced positive affect, improved satisfaction in relationships, and diminished anxiety in couples facing the diagnosis [314]. More recently Schirda et al. [199] reported that trait mindfulness was correlated with higher QOL amongst people with MS, that the effect was mediated by better emotional regulatory skills, and moderated by pre-existing depression. In non-MS populations, Kuyken et al. [197] have described how improvements in mindfulness and self-compassion mediate beneficial effects on mental health and resilience to relapses amongst people with recurrent depression, and Nyklicek and Kuijpers [315] have reported that enhanced mindfulness mediates stress reduction from training in MBSR amongst people who are stressed. Being more self-compassionate is also associated with greater resilience to stress, anxiety, and depression in people with other long-

term neurological conditions [316], but more research is required to define clearly what impact, if any, adoption of this attitude has among people with MS.

6.5.7 Strengths and weaknesses

A major strength of this feasibility study is that it is embedded in a larger body of research for the thesis, based on the MRC guidance [19]. By using mixed-methods, the findings from the RCT can be combined with those from the parallel process evaluation, specifically relating to participant and instructor feedback from taking part in MBSR. For example, semi-structured interviews can explore how participants experienced the course, the perceived effects, and possibly provide an explanation as to why treatment adherence was sub-optimal. Such data can be used to inform accessibility, acceptability, and implementability of MBSR for people with MS.

The major limitation of this study was its small size. However, this is acceptable in a feasibility study such as this. Not having an active control group such as a sham MBSR approach, like that developed by M^{ac}Coon et al. [317], or a group/ duration/ homework-matched CBT-style intervention, or similar, is another potential drawback. However, the MRC guidance [19] suggests that introducing an active control too early in the pilot/feasibility process can obscure findings at this stage. Other limitations include the limited spread of ethnicity amongst participants, the study taking place only in Scotland, and not including a biological outcome marker for stress.

6.5.8 Implications for practice/policy/future research

Given the pilot/feasibility nature of this study, these results are not generalisable to the population of people with MS at large, and clinicians and researchers alike should exercise caution when considering using the findings from this study to inform practice. What the findings do demonstrate is that, despite the broad feasibility of MBSR and trial procedures for people with MS, further optimisation work is necessary, in order to improve engagement, uptake, and measurement of treatment effects in this context.

Eligibility criteria appear to be acceptable both to referrers and potential participants, with only small numbers deemed ineligible on screening by the researcher. Retention

rates indicate that people with MS are willing to be randomised to either intervention or wait-list control groups. Despite the large volume of measures included in the participant questionnaire, there were no participant complaints, and missing values were not prohibitive when performing the a priori statistical analyses. The feasibility process has allowed collection of data for a range of relevant outcome measures. These findings can be used to optimise the intervention and its measurement.

Although large and stable beneficial treatment effects were evident in those receiving MBSR at three-month follow-up for positive affect and anxiety, initial large improvements in stress and depression at the immediate post-intervention point fell to small and negligible at three-month follow-up respectively. Given the dearth of effective treatments for anxiety in people with MS [10], the beneficial effects from mindfulness training found in this study, alongside those reported elsewhere [177, 289, 305, 306], could form the basis of an argument for proceeding to a phase-3 trial with anxiety as the primary outcome. However, as demonstrated in Chapter 4, both anxiety and depression are very common in MS, with depression known to increase morbidity and mortality in MS and to diminish QOL [5, 57]. Other studies of MBIs in MS have found improvements in depression following mindfulness training with more stable treatment effects where interventions included tailored MBCT [305], or a combination of MBSR/MBCT [306], but less so when simply using MBSR [177]. Thus, proceeding to a phase-3 trial at this point may be premature.

Optimising the intervention might conceivably generate more stable treatment effects for stress and depression, and this could be explored via qualitative work examining participant and MBSR instructor views from those taking part. Potential modifications could relate to improving the acceptability of course content and/or delivery, and might involve the integration of regular follow-up/'booster' sessions, as there is some evidence that this can help to sustain beneficial treatment effects from MBCT in people with recurrent depression [318]. Further optimisation could focus on improving study outcome measures, with recent guidelines suggesting the Beck Depression Inventory (BDI) be used for detecting depression in people with MS, and the Center for Neurologic Study Emotional Lability Scale (CNS-ELS) for assessing emotional lability [83]. Further, given the mediating role recently described for

emotional regulatory skills for improving mindfulness and diminishing depression in MS patients, [199], a process measure of this construct could also be explored [319].

6.6 Conclusion

This study has demonstrated that delivering MBSR under trial conditions is feasible for people with MS in a UK NHS Integrative Care setting. Recruiting to target was feasible within three months, and rates of retention and follow-up were generally good. Treatment adherence was sub-optimal and initially encouraging beneficial effects on scores for negative stress appraisal and depression were not sustained beyond the intermediate assessment point. These factors raise important questions about optimisation of the intervention, and proceeding to a phase-3 trial at this stage should wait until these issues have been explored in detail and resolved.

Chapter 7 Qualitative research chapter

7.1 Summary

This chapter outlines the qualitative process evaluation that occurred in parallel to the RCT. It starts by setting out aims and objectives, which largely focused on gaining a deeper insight into participants' and MBSR instructors' perceptions and experiences of the MBI and how this knowledge could be used to understand more clearly potential barriers and facilitators to implementation. The methods used in the chapter are described along with justifications for their choice. Results are presented in diagrammatic and textual format, delineating four main themes that emerged from the thematic analysis. Following this, the findings are then conceptualised using an implementation theory – Normalisation Process Theory (NPT). Based on the findings, key recommendations are presented. Finally, the discussion compares the findings with the existing literature for the use of MBIs in people with MS.

7.2 Aims and objectives

The overall aims of this study were to explore the perceptions and views of people with MS participating in a MBI (MBSR) and to examine the potential barriers to and facilitators of implementing a MBI for people with MS. Specific objectives were to determine:

- Pre-course expectations
- Experience of the course
- Which aspects of the intervention worked and/or did not, and why
- What effects, if any, were noted by participants on their wellbeing
- What factors influenced participation, completion, and drop-out rates
- Barriers and facilitators to engagement, uptake, and implementation of MBSR in this population.

7.3 Introduction

Building upon findings from the RCT, the next task was to collect participant views on the MBSR course. This information was sought in order to inform decision making about the feasibility of undertaking a large-scale trial of MBSR in MS, and also to inform thinking about the wider implementability of such a service. This parallel process evaluation aimed to clarify issues about how the course was delivered and received, and how it might be improved, in order to meet best the needs of people with MS, and to increase its future implementability. This work was intended to complement and add to the learning from the quantitative feasibility findings from the RCT.

Research in other LTCs suggests that MBIs might help people cope better with chronic illness, by enhancing self-management skills, improving QOL, and helping to shape a more positive illness experience [320]. Aside from MBIs, other qualitative work suggests that people with MS value learning new self-management skills, particularly for dealing with the chronic stresses associated with the condition [62]. Identifying successful self-management strategies has been highlighted as a research priority for this group [12, 62].

Very little qualitative research exists addressing how individuals with MS find MBIs. Aside from Hankin [296], who provided just a cursory snippet from her conversations with couples facing a diagnosis of MS who took part in MBSR training, only Bogosian et al. [313] have reported substantive qualitative data in this area. Bogosian et al. [313] reported on thematic analysis findings from 15 semi-structured participant interviews, where participants had taken part in a Skype-delivered MBCT programme for people with progressive MS. Bogosian et al. [313] undertook both deductive, and inductive analyses. The deductive analyses attempted to understand potential treatment mediators, whilst the inductive analyses were interested in participant experiences. Deductive findings focused on finding support for the potential role of acceptance, decentring, self-compassion, and self-efficacy. Inductive findings reported that participants valued the peer support that came from being part of a group, that the course instructor was an important part of their experience, and that

some participants were not clear about what to expect from taking part in a MBI [313].

Implementation is a complex phenomenon, whereby a new intervention makes the transition from theory into practice [321]. Potentially, it requires adaptation to take place on multiple levels, involving a range of stakeholders [321], and can be a protracted process [322]. On the '*macro-'* level, it can necessitate socio-politico-cultural change; on a '*meso-'* level, teams working together differently; and on a '*micro-'* level, it involves individuals [321]. Thus, there are multiple potential barriers to success in the process of implementation [323]. Implementation forms a key component of the MRC guidance [19] on developing and evaluating complex interventions to improve health. The guidance suggests that the study of implementation processes should be theory-driven, and that it should not be viewed as the final step in new health service development [19]. Instead, implementation should feature as a consideration throughout. This parallel process evaluation considered implementation of a MBI for people with MS. It was theory based, drawing upon information from multiple data sources, including qualitative participant and MBSR instructor feedback, alongside the range of information already collected from the quantitative aspects of the RCT.

7.4 Methods

Following completion of the MBSR intervention in October 2014, a series of 19 semi-structured interviews was conducted. In order to include as broad and representative a spread of views as possible, everyone who agreed to take part in the interview process was interviewed. This meant that 17 course participants and the two course instructors were interviewed. Interviewees comprised a range of participants of different age, gender, SES, and disability level, covering both those that completed the course (n=13), and those who had dropped out (n=4).

The interviews were conducted face-to-face, in a research office at the NHS CIC, and used a topic guide that had been developed and agreed with the researcher's supervisors. Questions were similar, though not identical, for both participants and MBSR instructors. The interview questions were informed by NPT and covered the

exploration of broad areas pertinent to stakeholder engagement and uptake of the course, such as pre-course expectations, experience of the course, the meditation practices, context, course logistics, and barriers and facilitators to participation (see Box 7.1 and Box 7.2 below, with questions mapped to NPT constructs).

Box 7.1 Semi-structured interview questions – Participants

1) How did you find the MBSR course? What were your expectations? (Coherence)
2) What worked well in the MBSR course? What didn't? What are your reasons? (Reflexive monitoring)
3) Was the MBSR course helpful or not? In what way? (Reflexive monitoring)
4) Was being in a group an advantage or disadvantage for you? Can you please explain your answer? (Collective action)
5) How did you find the setting for the class? What are your reasons for this? (Collective action)
6) Were there any barriers to your participation (both in relation to attendance or completion of tasks)? (Collective action)
7) What encouraged you to attend and complete home practice tasks? (Cognitive participation)
8) What are your thoughts on the duration of the course? The time the course took place at? (Collective action)
9) What were your experiences of having the home-practices? Were you able to complete the self-study assignments or not? What factors influenced how much time you spent on the home-practice assignments? (Collective action)
10) Have you noticed any differences since completing the MBSR course? If so, what? (Reflexive monitoring)
11) What aspects of the MBSR course were most/least helpful and why? Can you suggest improvements for future courses? (Reflexive monitoring)
12) Would you recommend MBSR to other people with MS? Why? (Reflexive monitoring)
13) Since completing the MBSR course, have you noticed any effects (positive or negative) on your sense of physical wellbeing? If so, what? (Reflexive monitoring)
14) Since completing the MBSR course, have you noticed any effects (positive or negative) on your sense of mental wellbeing? If so, what? (Reflexive monitoring)

Box 7.2 Semi structured interview questions – Instructors

1) How did you find facilitating the MBSR course? What were your expectations? (Coherence)

2) What worked well in the MBSR course? What didn't? What are your reasons? (Reflexive monitoring)

3) Do you think the MBSR course was helpful for participants or not? In what ways? (Reflexive monitoring)

4) Was facilitating the course as a group an advantage or disadvantage for you? Can you please explain your answer? (Collective action)

5) How did you find the setting for the class? What are your reasons for this? (Collective action)

6) Were there any barriers to you in facilitating this course? (Cognitive participation)

7) Did you encourage participants to attend and complete home-practice tasks? If so, how? What kinds of barriers to attendance and completion of home-practice tasks were mentioned by participants? (Cognitive participation)

8) What are your thoughts on the duration of the course? The time the course took place at? (Reflexive monitoring)

9) What were your experiences of setting the home-practices? Did you feel that completion of the standard self-study assignments were realistic or not in this current group? What factors influenced how much time you recommended for the home-practice assignments? (Collective action)

10) Have you noticed any differences in yourself as a mindfulness facilitator since completing the MBSR course? If so, what? (Reflexive monitoring)

11) What aspects of the MBSR course do you think were most/least helpful for this group and why? Can you suggest improvements for future courses? (Reflexive monitoring)

12) Would you recommend MBSR to other people with MS? Why? (Reflexive monitoring)

13) What are your thoughts on factors influencing dropouts' from this study? (Reflexive monitoring)

The qualitative data analysis in this chapter was informed by the framework approach to thematic analysis [211]. NPT [214] was the underlying theoretical framework that informed conceptualisation of the analysed data.

For a detailed timeline of research activities see Appendix J.

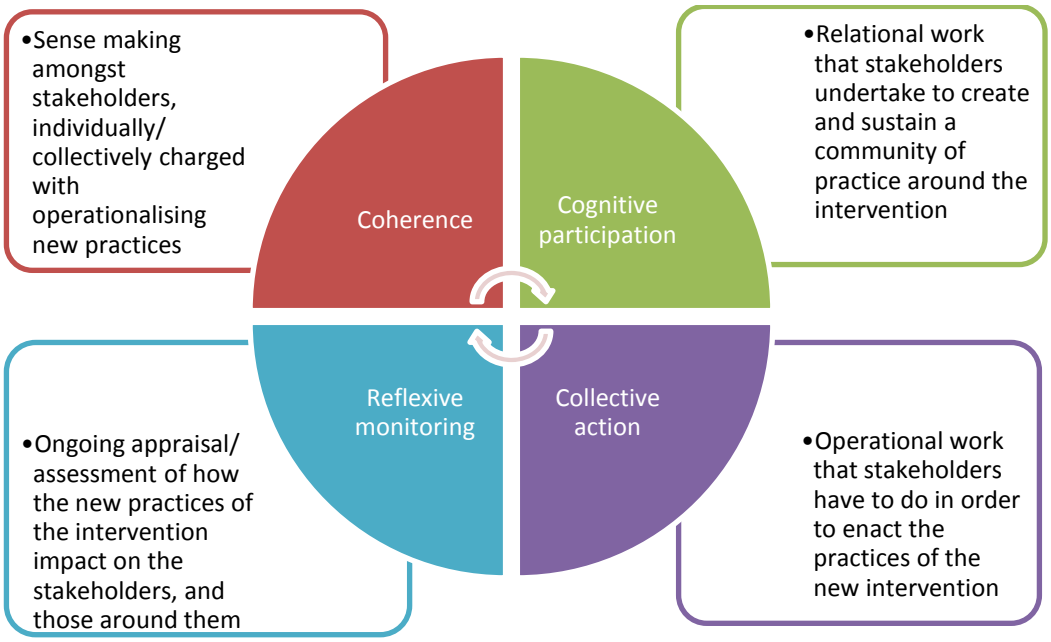
The key steps of a framework approach are outlined below in Table 7.1.

Table 7.1 Components of the Framework Approach

Components of the framework approach to qualitative analysis	
1. Data management	Familiarising oneself with the data via repeated reading
	Identification of preliminary themes/categories
	Development of a coding index
	Allocating the data into categories/themes in the coding index
	Iterative refinement of preliminary themes with repeated reading of the data
2. Descriptive accounts	Summarising then synthesising the range and variety of coded data
	The development of abstract concepts
	Modelling patterns/associations between themes and concepts
3. Explanatory accounts	Constantly referring back to the original data to ensure explanations are grounded in the views of the interviewees', thus reducing the chance of misrepresentation
	Making interpretations and founding possible explanations for emergent themes and concepts
	Mapping concepts and themes to the empirical literature and evidence base

Following completion of the thematic analysis, emergent themes were subsequently reviewed under the theoretical 'lens' of NPT, which has four key domains (each of which has four further sub-domains) (Figure 7.1). Practically, this process meant re-visiting the emergent themes that had already been generated through the thematic analysis, and assessing how they might fit (or not) with the NPT domains. Each of the four main domains and their respective sub-domains were thus tested against the thematic analysis data for goodness of fit. Results for the NPT analysis are thus presented following the thematic analysis results.

Figure 7.1 Normalisation process theory (NPT) core constructs



7.4.1 Thematic framework analysis. Stage 1 - Data management

7.4.1.1 General overview

Interviews were transcribed verbatim, and then checked by the researcher (RS), who listened to the interview audio files whilst simultaneously reading through the transcribed word files, making short notes and memos in the page margin. The researcher's two supervisors independently read through a randomly chosen, un-annotated transcript and made their own notes during this process, with all parties reconvening at the next supervision meeting to discuss their preliminary thoughts and findings. This introductory process allowed comparison between the researcher's notes, and those of his more experienced colleagues. The meeting fostered discussion on the importance of researcher reflexivity at this stage, especially around the common tendency of inexperienced qualitative researchers to over-interpret the data

early on in the analysis, and the need to reflect routinely on any underlying assumptions about the meaning of the data.

The next stage involved detailed immersion in the data. The researcher returned to the original data, reading through un-annotated transcripts, making notes on participant experience as close as possible to the original words and phrases used in the interview ('in-vivo codes'), which would later be used to develop data categories. Similar categories were eventually grouped together to allow the development of initial themes. As the researcher worked through the 19 transcripts, a separate file was kept which allowed the researcher to list initial themes that were emerging from the data. As this process unfolded a coding index began to develop. Due to the different emphasis of the questions in the respective semi-structured interviews, separate lists of codes were initially documented for the participants and the MBSR instructors, with a view to the possibility of merging/triangulating data at a later stage in the analysis. Through this process of immersion the researcher was increasingly able to see recurrent themes emerging, but remained cognisant throughout of two points: a) the need to remain distant from any theoretical standpoint (such as a bio-medically informed view of MS and/or mental health), and b) that the index was subject to change as the iterative process of analysis continued.

Data was thus arranged into thematic headings for each interview. At this stage, participant codes numbered 45, and those of the instructors' numbered 14. Following completion of this stage, it was important once more to cross-reference the findings with the supervisor's findings (Professor Stewart Mercer - SM), to check the reliability of the data [208], and again ensure that no underlying assumptions or interpretation had been applied to the data. SM reviewed a further two interview transcripts, noting emergent themes/concepts in the process. These were then cross-referenced with the index of codes and associated themes identified by the researcher and a new and refined coding index emerged. By this stage, the researcher was able to draw up a coding index for each group of interviews, with participant codes reduced to 28, whilst those for the instructors' numbered 15. Following this, the researcher went on to develop a merged index, where both participant and instructor findings co-existed under higher order themes, each with associated sub-themes. This process took place using word files, both for the transcripts and for the emergent theme

documentation of each interview, allowing memoing and iterative reflection to take place throughout.

For details of the final coding index, see Appendix K.

7.4.2 Stage 2 - Descriptive accounts

The next step involved summarising and synthesising the original interview data in descriptive terms. The option still remained thereafter to offer an explanatory account, with themes also being organised further in chart format, where emergent patterns could be sought in relation to important demographic data, including such items as participant age, sex, SES, and disability level. Critical thinking and reflexivity remained paramount during this stage, and care was taken not to stray beyond the veracity of the participants' own accounts when seeking links and extrapolating into more abstract conceptual views of the data.

When constructing the thematic matrix for the data, the guidance suggested in the methodological overview by Ritchie and Lewis [211] was followed. This meant that the matrix had to ensure that the data it contained remained 'conceptually pure', i.e. remained true to the original participant accounts, and avoided overlap with related themes, where possible, thus making meaningful distinctions between findings, and providing illuminating content.

The next steps involved:

1) Detection of substantive content and dimensions
2) Categorisation, which meant description and refinement of the findings
3) Classification, or the grouping of information into categories, which necessitated a subtle mode of abstraction

7.4.3 Stage 3 - Explanatory accounts

At the stage of developing explanations, the researcher interrogated the data in different ways, in order to ascertain what might be influencing or causing the

observed phenomena. This was initially undertaken individually, and subsequently critiqued, refined, and finessed during research supervision meetings. For this stage of the analysis, the researcher reflected carefully upon interpretation that could be based either upon whole group analysis (i.e. a single unit), or a participant-based group analysis (taken in the context of the whole). For example, explanations could come directly from participants themselves (either dispositional or situational), or from inferences drawn by the researcher. Thus, attempts at explanation were driven from first reflecting back on the raw data as a whole, and then to the various different analytical stages, in order to ensure once again that the data was not being made to fit a particular interpretation.

Following on from this, an attempt was made to ascertain whether any emergent typologies could be identified which might explain the operation of the various concepts derived from the original data. Possible typologies are illustrated in the Results section, and the thematic matrix is available in Appendix L.

An important consideration throughout was the role of the researcher as both interviewer and data analyser. Carrying out the research in this manner was necessitated by the limited resources that were available for the PhD study – had the option been available, it might have been preferable for another individual with no connection with the analysis to carry out the interviews. The approach used has inherent potential for bias, but specific and consistent steps were put in place in an attempt to minimise this possibility. For example, the potential for bias and the importance of reflexivity were discussed between the researcher and his supervisors from an early stage [208]. Any suspicion that bias might have crept in to the analysis was discussed openly during regular supervision meetings, where transcripts, coding, and emergent themes were reviewed between the researcher and his supervisors.

7.5 Results

Amongst the 17 participants interviewed, the mean (SD) age was 45.06 (9.34) years, and 15 of the 17 (88%) were female. The mean (SD) deprivation decile was 5.06 (2.74), with a range across participants from decile 2 to decile 10 (where lower numbers indicate less deprivation). In terms of highest educational attainment, 3/17

(17%) had a secondary school education, 4/17 (24%) had a college education, and 10/17 (59%) had completed a university education. The mean (SD) EDSS [117] score of disability amongst participants was 4.59 (1.84), which equates to '*Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m*'. In terms of MS phenotype, 15/17 (88%) had RRMS, whilst the remaining two had PPMS. With regards to comorbidity, the mean (SD) number of other LTCs amongst participants was 4.00 (2.89), whilst the range extended from 0-9 conditions. Eleven out of seventeen had at least one mental health condition (range 1-3). Of those interviewed, 13/17 (76%) met the cut-off criteria of attending four or more MBSR sessions required for course 'completion', and the median (range) amongst all participants interviewed for session attendance was 7.0 (7.0). The MBSR instructors were both female medical doctors with backgrounds in General Practice, but working full time in Integrative Medicine. Table 7.2 outlines baseline demographic data for the interviewed participants.

Four main themes emerged from participant and MBSR instructor accounts:

1) 'Coming together for the course – everyone has MS'
2) 'Doing the work of mindfulness'
3) 'Getting it, or not'
4) 'Moving forward and improving the course'

These themes largely reflected the process that participants and the MBSR instructors had experienced through engaging with the intervention, but also included details regarding the experiences of those (4/17) who had discontinued taking part in the course. Each of the four main themes was broad in its coverage, with several underlying sub-themes in every case. These are discussed in detail below.

Table 7.2 Participant characteristics and number of sessions attended

No.	Age in years	Sex	Ethnicity	Deprivation decile	Education	EDSS score	Type of MS	Comorbidity count (number of mental conditions)	Number of sessions/8 attended
P1	52	F	WS[ϒ]	2	University	4.0	PPMS*	3 (1)	7
P2	41	F	WS	2	University	4.0	RRMS°	3 (1)	6
P3	54	F	WS	9	University	5.5	PPMS	0 (0)	8
P4	36	M	WS	3	2y School	2.5	RRMS	9 (3)	7
P5	65	F	WS	8	2y School	5.0	RRMS	9 (2)	7
P6	44	F	WS	8	University	6.5	RRMS	5 (2)	7
P7	52	F	WS	2	College	6.5	RRMS	5 (1)	3
P8	34	F	WS	3	University	3.5	RRMS	5 (1)	7
P9	48	F	WS	5	2y School	7.0	RRMS	1 (0)	2
P10	43	F	WS	7	University	7.0	RRMS	1 (0)	7
P11	27	F	WS	6	University	6.0	RRMS	4 (1)	8
P12	38	F	WS	3	College	2.5	RRMS	5 (2)	5
P13	46	F	WS	3	University	4.0	RRMS	8 (0)	1
P14	32	F	WS	10	College	4.0	RRMS	6 (2)	8
P15	40	F	WS	4	College	1.0	RRMS	2 (0)	1
P16	44	M	WS	8	University	6.5	RRMS	0 (0)	7
P17	36	F	WS	3	University	2.5	RRMS	2 (1)	6

*PPMS – Primary Progressive MS ; °RRMS – Relapsing Remitting MS, EDSS – Expanded Disability Status Scale; 0 lowest level of disability – 10 death. ϒWS – White Scottish ethnicity

7.5.1 Theme 1 'Coming together for the course – everyone has MS'

The first major theme 'Coming together for the course – everyone has MS' reflected a group of 27 people all coming together for the first time to learn about the use of something new i.e. mindfulness in MS. The four subthemes reflected what participants and the MBSR instructors had expected of the course prior to taking part, what they had to do in order to be at the course, how they had experienced the venue, and what being part of this unique group had been like for them (Figure 7.2).

These themes reflected that the course marked an 'event' for those taking part, involving some degree of not knowing what to expect or how to prepare, of becoming acquainted with their meeting ground for the next eight weeks, and coming together to learn mindfulness as a group entirely made up of people with MS.

Figure 7.2 Theme 1 *'Coming together for the course – everyone has MS'*

7.5.1.1 Pre-course expectations – why people were taking part in MBSR

Mindfulness was new for most people (13/17) and most did not know what to expect from the course. Some were sceptical (5/17), whilst others were more hopeful of deriving some benefit (7/17). One participant noted that the fact it was a 'clinical trial' for people with MS had acted as a motivator to her taking part, whilst another had thought the course would be quite MS-specific in its content:

> '*I thought if I get anything out of it, it would be a bonus, I wasn't really expecting too much I was kind of sceptical because I hadn't really done anything like that before'* (**P10**)

> '*I hoped that there would be methods to try and cope with pain, stress, lack of sleep*.' (**P13**)

For the instructors, pre-course expectations were influenced by prior teaching experience, assumptions about the MBSR course, assumptions about people with MS, along with the fact that this was a research project focusing on a specific condition:

> '*I expected it to be the same as all the other groups.. ..we have done it with people with chronic fatigue before and again it's got a particular atmosphere about it, a very heavy atmosphere.. This had a kind of hypersensitive atmosphere.. ..slightly different than a mixed group.. ..it does make it different yeah*' (**I1**)

> '*..because they had been very specifically recruited, they'd had a long interview with you beforehand.. I was expecting a fairly high degree of motivation'* (**I2**)

7.5.1.2 Being prepared and getting there

It was apparent from feedback that taking part in the course meant more than just turning up for two and a half hours each week, especially so in the context of disability. Participation required a lot of preparatory work, such as arranging time off work, organising childcare, securing transport, modifying routines in the home, and then dealing with the journey to and from the venue.

One participant who ambulated with elbow crutches highlighted how getting there and finding parking was a source of distress:

> '*Parking was a real trauma, I had to leave the house an hour earlier to get here and to get a space and I found by the time I actually got into the reception area I was stressed'* (**P6**)

Because of the difficulties with parking, some participants opted instead for public transport, significantly increasing their journey time.

7.5.1.3 Course context – getting it right

The setting for the course, the NHS CIC, seemed to have had an impact on participants. For some (6/17), coming to the centre demarked quite a contrast to other hospital settings that they were more accustomed to:

> '*I think the hospital itself is lovely, it is. Right away you don't think of it as being a hospital actually it's much nicer, which makes you feel more relaxed, it's less clinical and yeah that's it.. ..I think having the surroundings here is much more peaceful.. ..It was quite pleasant and you were pleasantly surprised .. and oh it is actually quite lovely here .. and being able to see the garden*' (**P2**)

The first MBSR class took place in an upstairs seminar room, which was accessible either by a flight of stairs, or by a lift. The room had been chosen for the course because of its size, and availability. However, some important issues had been overlooked, again with a particular emphasis being placed on disability awareness:

> *'..as the day progressed, started and progressed there was things that kind of flagged up and kind of irritated me quite early on. One was the distance between the room where it was being facilitated and the bathroom.. The second thing which was one of my bugbears .. when you came into the room there was a semi-circle of chairs and literally each arm of each chair was touching each other with no gap..*'. (**P13**)

Another issue was the centre policy of not allowing drinks to be brought into the room, which some participants (2/17) complained about as it meant if someone had a dry mouth due to a medication side-effect, they could not immediately have a drink, or if someone needed to take medication during the class, no fluids were on hand.

These observations were fed back by the participants to the instructors via routine course session feedback forms. Based on these, the instructors moved quickly to make things right for the group the following week. This led to a subsequent change of class location to a ground floor room, which necessitated involving the wider MDT in the Centre, and shifting a Yoga Therapy course that was running at the same time. However, it was clear that participants appreciated this response:

> '*They kind of said that: "Obviously it was highlighted to us last week and we hope this is better" and they apologised and things like that so it wasn't just brushed under the carpet or ignored and I thought that was good .. I think everybody in the group appreciated that*' (**P17**)

7.5.1.4 Becoming a group

One participant commented that the group structure was more acceptable to him than having to work on a one-to-one basis or in smaller groups, as he found this less daunting, but others (8/17) expressed preferring the group format. Participants appreciated that the issue of confidentiality was raised early on by the instructors (*'What happens in the room stays in the room')*. A few participants (3/17) had worried about being asked to speak in public during course introductions. The instructors' introductory exercise, that they normally used as an 'ice-breaker', introducing the person seated next to you and what you both had in common, seemed to backfire, producing an almost uniform response of '*We both have MS!*'. Many participants (7/17) spoke of their apprehension about being in a room full of people with MS, with a spectrum of ability levels:

> '*I'll see somebody far more disabled or affected with MS and it hurts me too because it's like this could be your future'* (**P13**)

Despite the difficulty in seeing others more or less disabled, all of the participants reported valuing being part of the group, with comments focusing on appreciating being able to see/hear others' thoughts/views on their experiences. Many participants (8/17) expressed not actually knowing many other people with MS, and appreciated the opportunity of being able to come together in this way.

Despite these initial forebodings, the fact that everyone in the group had MS seemed to facilitate a sense of trust and safety:

> '*I just felt the same as them, even although everybody didn't have a crutch or an eye problem like myself I still would have just went, everybody understands, that's it*' (**P11**)

7.5.2 Theme 2 'Doing the work of mindfulness'

The second main theme that emerged was 'Doing the work of mindfulness', and this captured various sub-themes relating to what taking part in the MBSR course actually involved for people. Sub-themes included what it was like for people with MS to experience the mindfulness approach of getting in touch with their senses, sensations, disabilities, and diagnosis of MS; how the participants made sense of the mindfulness practices, together as a group; how participants experienced the mindfulness practices on their own, away from the course; and what sustained or prevented their continued participation (Figure 7.3).

Figure 7.3 Theme 2 '*Doing the work of mindfulness*'

7.5.2.1 'Coming face-to-face with MS: senses, sensations, and disabilities'

The course commenced with the 'Raisin Exercise', which involved everyone being handed a raisin to hold in his or her hands. Everyone was then guided through a set of instructions designed to help notice in detail various different aspects of the experience relating to the raisin, such as size, texture, contours, and eventually taste. The raisin exercise is designed to bring an increased sense of awareness to mundane aspects of experience, and how these can be taken for granted [13]. Most people (15/17) did not comment specifically on the experience, but one individual described it as *'weird'*, whilst another found the focus it brought to her hands very distressing:

> *'..I thought oh great, of all the things to do my hands are the worst affected, I have the most pain in my hands 24/7 and I'm being asked to hold a raisin, but suck it up, these things happen when you've got MS..'*. (**P13**)

This was an unexpected and difficult experience for the instructors:

> '*I haven't seen people cry at the raisin exercise before now so that was quite difficult and from one woman with the raisin exercise there was a very direct challenge of: "Am I right in thinking you're asking us to really face our experience?".. and we were like "Yeah, being present with your moment-to-moment experience is what we are asking you to do" and she said: "That is so not what we do, what I do, how I manage this, this isn't going to work for me".. So, there was one quite strong character who was very challenging and.. Well, it threw me a little bit*' (**I1**)

Both of the instructors described their prior assumptions about MS. They felt that it was a difficult diagnosis that carried a strong illness identity. They both felt mindfulness would be very beneficial for people with MS, in helping participants 're-connect' with their bodies in a pleasant, and relaxing way. One of the instructors (**I1**) spoke about carefully bringing people close to their tolerance limits, in such a way that everyone could feel included, regardless of differing ability. Several participants (9/17) commented on the instructors' style as being supportive for the mindfulness

practices, but for other participants (4/17) doing the practices accentuated a sense of disability:

> '*In the other exercise the one that we were doing that all these kind of things with the hands again it wasn't suitable for everybody to do that in the class because I can't move this right hand so exercises like that accentuate the disability that I have and I didn't like it .. I just didn't like the experience of it.*' (**P6**)

> '*On a personal matter, because of the tremor in my right hand I can't write now, so if there's anything involving writing.... I found it personally embarrassing to me because it was barely legible, so I didn't like they* [those] *parts of the course*.' (**P16**)

Another dimension touched upon by the instructors related to the idea of bringing compassion to a struggling body, and the role that compassion might take in dealing with the condition:

> '*We did teach compassion practices as well and I think people found that useful, and actually it was a useful practice, but it was also a new and interesting idea that once one demonstrates compassion towards oneself, and I think people actually, you know, this was, actually brought up you know, that in MS the body is turning against itself and it's interesting to try and be, actually advocate kindness towards the body*.' (**I2**)

7.5.2.2 Making sense of the mindfulness practices, together in the group

Although most participants did not have prior experience of mindfulness specifically (13/17), several (11/17) had prior experience of meditation and/or yoga. This may have shaped their impressions of mindfulness. One participant who practised Sahaja Yoga described how the technique never focused on her condition (MS), whereas the MBSR session she attended did, which she thought was a mistake. Another, a qualified Ashtanga Yoga instructor, described the course content as very '*basic*', and

he seemed to be making sense of it using terminology from the area that he was more familiar with, talking of experiencing his '*Prana*' (A Vedic concept relating to '*life force*', or '*energy*' associated with the breath - [324]).

One individual, who had one year previously taken a short introductory mindfulness course run by a trainee psychologist at a nearby hospital, was surprised at the depth of the compassion practices in the current course:

> *'Yeah, those ones in particular were about self-compassion or about loving yourself and I found those ones quite difficult. They didn't drag up history I wouldn't say, but I guess the very fact I was finding them difficult, I was looking for the reason why I was finding them difficult and that then went back to previous things that I suppose have shaped me, who I am today, going back to having been abused as a youngster and my self-image I suppose as a result of that'* (**P12**)

However, as stated previously, mindfulness specifically was a new concept for most, especially in the context of managing symptoms associated with MS. Some (7/17) commented that they were still coming to terms with the experience, and one participant commented that she particularly liked the meditation practices because they were in some way less '*artificial*' than taking medication.

In particular, several people (6/17) found it hard to make sense of mindful walking. One participant described feeling quite taken-aback at being asked to do it:

> '*Yeah, yeah well because my mobility is quite bad the part of the course the mindfulness walking I just thought that was bizarre to say the least, asking people with MS to walk I thought that was bizarre.. .. Well like being asked to walk, I kind of took the huff .. I sat that one out.. I said to* [instructor] *you know I said "I'm not going to do this and then after they had done it I opened up a conversation with the rest of the group around that I openly said to them I felt that was really bizarre, wrong, to ask people with MS to walk*' (**P16**)

Others also found the mindful walking challenging in the group, but less so at home (5/17) where they felt there was more space to explore the experience. These participants reported being quite unsettled by the practice initially. However, when practising away from the course, they seemed to be deriving useful learning from it, either through exploring the process of balance, the different sensations on different underfoot surfaces, working to stop themselves from walking on the sides of their feet, or by challenging themselves to climb stairs without stopping. One participant summarised her thoughts on mindful walking:

> '*I think everyone in the room didn't like it.. everybody kind of freaked thinking, even although I'm saying everybody had MS we all freaked thinking "I feel ridiculous doing this and staggering about the place and walking like a zombie round about a room". Right that was my thoughts, so that .. but I've got benefit from it, I've realised, at the time I didn't think so, I just thought it was "stupid, not doing this, that was ridiculous anyway" and then the homework was to keep doing it and I did struggle with it..*'. (**P11**)

A normal part of MBSR involves the 'enquiry process', where participants are invited to reflect and feedback on their experiences with the group [137]. This is used as a teaching tool in MBIs, where the instructor may pick-up and elaborate upon key mindfulness concepts for the benefit of the group, and is not designed to be instructive, or critical [137]. However, the enquiry process was met with mixed feelings from participants. A few (3/17) were not sure how to answer the questions. For one it was too intense, especially in the context of her fatigue:

> '*I just didn't have the energy to be questioned in that detail, I was happy to give like a one or two-liner but I just didn't have the energy to be drilled down, and down, and down, and down.*' (**P6**)

7.5.2.3 Making sense of the mindfulness practices on one's own, away from the course

Both instructors felt strongly that home practice was a very important part of the course, basing their assumptions on literature they had read suggesting that those who

practise most derive the most benefit. They reported concern that very few participants were actually doing the home practices in the early weeks of the course, a time that they thought formative and particularly important. They saw the home practice as being the responsibility of the participants.

Many participants (8/17) spoke about the home practices and their attitudes towards them, and views varied. One participant felt compelled to complete the home practices, given that a '*doctor was advising it'*. One participant described feeling a sense of rebellion at being asked to do '*homework*', whilst another described wishing time doing the home practice was passing more quickly. Another participant described assuming that she would have a preference for shorter home practices, and was surprised to find that this was not necessarily the case, whilst another had an initial loathing towards it, which was eventually superseded by a change to looking forward to it as she started to feel benefit.

Discussion and views around home practice covered a great deal of issues relating to practical barriers and facilitators in this area. For one participant the simple fact of not having a CD player at home presented itself as an immediate barrier, which she was able to overcome by borrowing from her ex-husband. More common comments related to making time and space for the practices. Being free from duties and/or distractions in the home featured repeatedly.

7.5.2.4 Staying present, or dropping-out - sustaining participation

Despite the difficulties experienced from the first MBSR session, several participants (7/17) commented on their commitment to see the course through:

> '*I suppose the group, the group as well sort of inspired me to go along.. ..I just knew that I had to give it a go and I had to see the programme through.. .. I wanted to get the full benefit of the course and to my mind if you're coming to one and not another then you don't get the full benefit of it*' (**P1**)

One participant described a sense of obligation towards the course organisers', despite encountering significant health problems in the course of events:

> '*Yeah I'd kind of, I felt obliged to because you guys set this up I thought well at least I had to do that, it was just, just the one I missed was I couldn't actually, I couldn't actually walk at that point at all so that was that one, that one finished*' (**P16**)

Attendance on the course was varied, with completers citing various reasons for non-attendance, such as inter-current illness in themselves or significant others. For a couple of participants (2/17), keeping up, or in mindfulness terms '*staying present*' with the practices took on even more of a challenge by the occurrence of a MS relapse during the MBSR course. For one participant, who was in the process of changing her DMD regime, this facilitated a new and more favourable experience:

> '*I came off one* [MS medication] *so I needed a gap before going onto the second and I unfortunately had a relapse in that period, not a particularly severe one, but I feel that I have recovered far faster from that relapse. Now, whether that's me just thinking that that's what's happened, but during the relapse.. ..very different I didn't get down, I didn't get depressed the way that I have previously about friends or family having to help out .. Before I've really struggled with that, I've become angry, aggressive, as a result of being depressed about it. I guess I didn't have that this time. I was fed up, I wasn't happy about having a relapse, wasn't happy I couldn't open a bar of chocolate very well one day when my hand wasn't working, but I didn't get down about it the way that I have before, and I genuinely think that mindfulness has helped with it.*' (**P12**)

For another, having a relapse acted as a barrier to keeping up the home practices, impacting quite negatively on his outlook:

> '*That's when I stopped doing the practices, when that started, because it was pretty severe, it was. I hadn't experienced this before, there was a lot of new things .. I kind of took the huff and thought "What's the point?" Having discussions with the people in the group I thought I was telling them what I was going through you know.. They were saying "Well this is probably the*

> *best time to do it" and I was like "Yeah probably" ..I was just like "Och what's the point"* (**P16**)

For some participants (4/17), the instructors acted as facilitators in helping them to engage with the practices, and encouraging them to attend the MBSR sessions. For others (4/17), it was family members or significant others that they respected, such as their MS Specialist Nurse, or their GP.

A majority of participants (10/17) were still practising since completing the course, although quantifying exactly how much and how often could not be determined clearly from their responses. One participant noted the difficulty of maintaining the practices without the incentive of a forthcoming weekly class. She revealed that she was still doing the meditations, but in a more narrow range than during the course. Another participant commented that it had been difficult following course completion, in that [you] went from an immersion in the routine to then being left on your own:

> '*I think, see because it's like practice, practice, practice, practice and you go to the group one and that's quite constant and all of a sudden it just goes stop'* (**P11**)

Some participants (4/17) mentioned that they would have liked for the course to continue, and that they were keen to keep coming by attending a fortnightly drop-in session held at the centre (open to all completers of mindfulness courses run at the NHS CIC and not specifically part of the current course), but for at least one participant, the fact that this was scheduled to take place in the upstairs seminar room served as a strong barrier to taking part:

> '*I think the fact that the mindfulness course is continued every 2nd Friday or something is good, but again it's up in that room so that's a barrier to me, I will not be attending and that's a shame that it's away up there*.' (**P6**)

The course was not for everyone. One of two male participants who dropped out following the first week could not be contacted again. The other divulged over the telephone that he had found the group format quite overwhelming. Another female

participant, who attended the first session only, expressed bemusement and frustration at the perceived emphasis on disability. This view was echoed by another lady who attended only two sessions, also feeling that there should have been emphasis placed on '*pushing one's limits'*, instead of simply accepting one's limitations/disabilities.

Feedback gleaned by the course instructors highlighted that seeing others more or less disabled, the intensity of the course, the perception that the course was not MS-specific, and the unacceptable venue set-up for the first week had all played a significant role in influencing dropouts. The instructors both remarked that through prior experience with teaching mindfulness they had recognised the need to have a pre-course orientation session to address expectations, and to make it easier for people to leave '*gracefully*', at an early stage. The orientation session had been dropped from this course, for pragmatic, resource constraint reasons. In this course, they felt that people arriving on the first day had been wary and uneasy, unprepared, and not really sure what to expect.

For those who dropped out from the course (3/17), the perceived focus of the mindfulness practices on acceptance of more negative aspects of experience, such as pain, functional limitations, or disability was a strong feature in their reasoning for leaving:

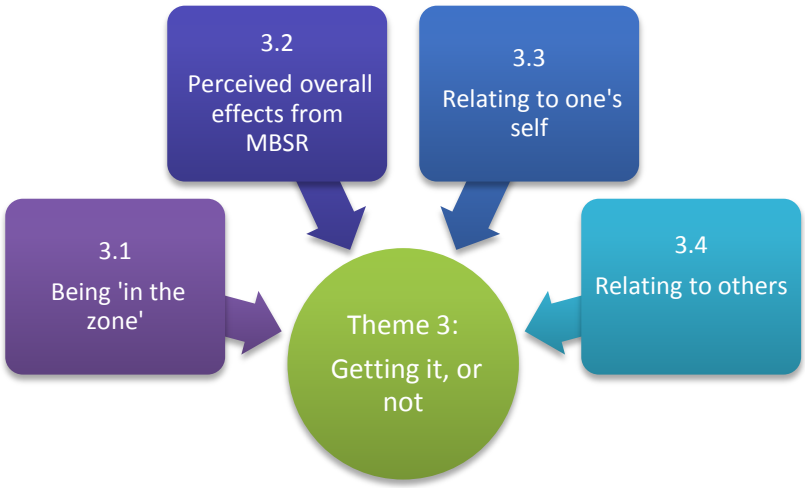
> '*I think it was great for some people but it just wasn't for me because I took MS all the way through I've always had a positive attitude, I've never let it get controlling me, so when I was sitting listening to everybody I thought "There's too much negativity in here". I'm not really into negativity, so that's why I thought: "No, I can't go back to that", because I needed more out of it'* (**P9**)

7.5.3 Theme 3 'Getting it, or not'

The third main theme covered how/what people got, or did not get from the MBSR course. Once again, there were several sub-themes that fell into this category, including what it was like being 'in the zone', or a meditative state of mindful awareness; the perceived overall effects of the mindfulness practices; how being

mindful impacted on self-care; and how being mindful impacted on relationships with others (Figure 7.4).

Figure 7.4 Theme 3 *'Getting it, or not'*



7.5.3.1 Being 'in the zone'

Participants who felt that they had benefited from taking part in the MBSR course repeatedly mentioned a qualitative shift in awareness during the meditation practices (7/17). One participant described a positive experience during a practice in the class setting, where something '*clicked*', and how this experience acted powerfully to facilitate her on-going engagement:

> '*Lovely, lovely, it was a great feeling. I think particularly the day I felt it kind of clicked for me was the day we did the Mountain Meditation and I just felt fantastic after that and it just felt so right! I just, and it's a great feeling, it really is a great feeling and I will miss it. Well, not that I have to miss it because I'm still doing it, but I think because it was new as well you know and it was lovely to feel kind of happy and excited as well'* (**P2**)

Another described a quite similar process, this time with the home practices, which prior to that point had seemed quite a chore. She mentioned the idea of '*buying into*' the practices, and how seeing a difference in herself facilitated this.

Another participant described an awareness of change in her experience, where habitual responding to a source of fear had changed into a sense of wonder at what is:

> '*I'm talking about like two minutes to actually appreciate things that you would never have done before. I'm terrified of birds, but during the course I found myself at the kitchen window being in awe of a Robin and it was amazing. It was as if nothing else mattered in those two minutes and it made me feel really good'* (**P8**)

There were further comments from participants (5/17) that seeing and hearing how others were experiencing the course helped with their own understanding and experience of the practices. However, for others (2/17), questions arose as to whether they were doing the practices correctly, although this lessened with time. For at least one participant, relaxation proved to be an insurmountable obstacle, as she felt that this was just not who she was.

7.5.3.2 Perceived overall effects from taking part in MBSR

The majority (13/17) of those who completed the MBSR course reported feeling better in a variety of ways. Of the more frequent reports, 13 people directly described feeling less stressed or more relaxed, and four people happier. One individual felt that she was finally getting back to being her old self:

> '*I'm going back to laughing or being the dolly person that I was before and that's the person that I liked, I didn't like that person that I turned into at all*.' (**P14**)

Another described feeling elated, with a new sense of wellbeing and optimism:

> '*I feel as if I'm much more in control of what's happening. I feel as if I can use almost like my mind to heal my body. I feel as if I no longer get stressed about things, I no longer worry, whereas I used to be a real worrier. I just, I'm quite accepting of things'* (**P3**)

From a physical perspective, several participants (5/17) reported feeling less pain during the practice:

> '*..It can help with the pain. I mean, I think you know, people may be quite sceptical at first, because I certainly was, but I would say to them"You've got to try it because it does help".. ..So, for example, in the Body Scan I feel quite light afterwards, quite, I think the pain goes away. It may not stay away, but for that time it goes away and that's great.. .. I feel like I can at times control the pain'* (**P2**)

For another, the practices were having a more lasting effect on pain and associated sensory disturbances:

> '*The numbness in my feet and my hands, I keep waiting for this. They're still burning at night. I notice that if I put it against my legs but I don't actually notice it in my feet if you know what I mean and last night they used to go into kind of spasms and things and last night it was cooler and I thought "Well my feet will be going all that horrible way" and they weren't, so there's been a definite improvement there, and my hands aren't so numb, they don't go so numb so quickly either*' ***(P5)***

For at least one participant, there was a change in how she related to sensory phenomena in her body:

> '*It didn't change the sensations as such, it changed my way of thinking about the sensation.. ..my thought process, I wasn't stressing about "Oh my goodness this is, there's a tingling here", I was more relaxed about it and I accepted it you know'* (**P1**)

Several participants (4/17) reported improvements in their walking, despite the initial difficulties mentioned earlier.

One participant, who dropped out after the first session, reported feeling mentally worse as a result of taking part in the course. She had various complaints about the

session she had experienced, centring on perceived organisational and attitudinal failings from those running the course, but in particular she emphasised an increase of pain in her upper limbs and how this had affected her mental wellbeing:

> '*My mental wellbeing has taken a wee dunt because the pain has increased and certainly that one day I attended here really highlighted my hands and the roll-on effect of that has been quite large, but it wouldn't be fair to say that my mental dunt is down to that one day. It's been a small proportion of it*.'. (**P13**)

Another participant, who dropped out after attending the first session, also reported briefly feeling quite low after attending the class, like she had a '*chronic illness*' and was destined for a wheelchair. Following discussion with her MS Specialist Nurse and a senior colleague at work, she decided that the course was not for her and immediately felt better.

7.5.3.3 Relating to one's self

Several participants described how a shift in awareness had led to a change in how they related to themselves (9/17). Many described having a realisation that they were being very hard on themselves (7/17), and that this needed to change:

> '*The course made me realise that I do beat myself up a lot and I don't feel as if I'm doing that now.. I think before I was very much like "I've got this wrong with me and that wrong with me", but thinking "well that is wrong with me but I can still do x, y and z". So, making me aware that maybe my body isn't 100%, but I can still do this and I can still do that and maybe one day if I couldn't do something as well, I wasn't putting myself down as much, because I would normally beat myself up about it'* (**P14**)

One individual described the process of recognising that her mood was becoming low and being able to intervene before it became worse. Another described a similar process of becoming aware of rising stress, and acting on it in the moment:

> ‘*Once I catch on that there's like there's something happening say, say if the wee one is running around and she's getting me quite uptight and I'm like "I need to pull myself back a wee bit here" and I'm like "Right, I'm going to do a quick breathing".'* (**P11**)

Another participant described how the realisation that she did not have to react to and follow her thoughts precipitated a positive change, which significantly improved her sleep:

> ‘*My whole mind is much calmer.. That settling the mind one, I really like that and I think yeah, I think my mind was a total jumble of all sorts of thoughts and worries and.. Oh there was one thing that really struck me, that one of the women* [MBSR instructor] *said "Thoughts are not facts".. ..I think I used to get everything in my head and like I would lie awake worrying about things and I would decide "Oh that's really bad" whereas that wasn't really bad, or "I should have done that, I should have said this, I'll need to try", whereas now I just do the cycle in my mind and I just don't even go there anymore and I don't dwell on things, I used to be a great one for worrying and dwelling on things so now I'm just much more, much, much calmer in my mind and yeah*.’ (**P3**)

One individual implied a more contemplative approach to challenges, stopping to think before responding, and another described recognising her limits in terms of how much she could give to others. Finally, one participant relayed the process of seeing unhelpful behaviours in herself, but also seeing the opportunity for change.

7.5.3.4 Relating to others

Several participants noted improvements in relationships over the duration of the course (10/17). One participant offered a quite profound insight into her change process of sharing her MS burden:

> ‘*Uh huh and it kind of made me realise that I have to deal with certain things in my life rather than just putting them on the back-burner.. ..Just*

> *relationships and things like with my parents and my husband, things that I don't tell people because I feel that it would hurt them or I put on like a strong confident person just because I don't want them to know how I feel, but actually, it's actually really important they know how I feel, because they can't help me unless they .. I've tried to do that more.., let more people into my life and stop having a wall around and it's helped me as well to have more real confidence, rather than more fake confidence, which is good, yeah I feel happier for that, because I feel like I'm being me more, rather than having just the big smiley face on all the time.*' (**P8**)

Various participants (4/17) described feeling closer to/more aware of their relationship with their children, whilst two revealed that their spouses had noted a positive change in their behaviour. One individual was using mindfulness techniques to help a cousin suffering with anxiety, whilst another taught the techniques to her elderly and infirm father who was struggling to come to terms with his declining capacity. Participants' generally described feeling more aware of other peoples' perspective, with more empathy, even compassion towards them. In one situation, where a participant had witnessed an apparent aggressive act from another partygoer, seemingly directed towards her, she described experiencing a new way of responding, which for her was more reflective and less argumentative:

> '*He's got all these pressures and I probably wouldn't have recognised that before. I was more aware of my surroundings and more aware that everybody has got something going on in their life and there's probably a reason to why he's hitting out.. ..As I say I would have probably, maybe not started an argument with him, but I would have been more confrontational'* (**P14**)

One participant commented how using the mindfulness techniques had helped her cope with family conflict. Another described greater tolerance towards other road users:

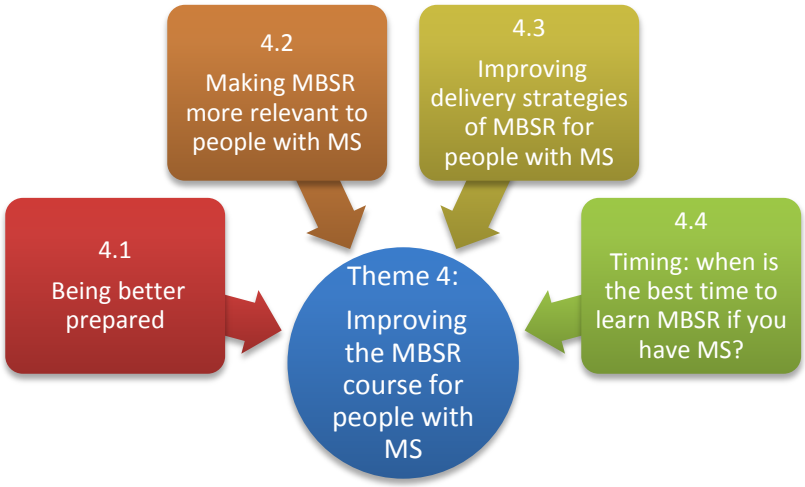
> *'I'm just thinking driving was a big one for me, where you know, where people cut you up or whatever and you start shouting or whatever, but I was more,*

more just "Let it go", I was definitely that sort of sense and as I say the people that I work with just too, just chilled out, more chilled out' (**P16**)

7.5.4 Theme 4 'Improving the MBSR course for people with MS'

The fourth main theme related to how participants and the MBSR instructors felt the course could be improved for people with MS. Sub-themes here centred on improved pre-course preparation; course content and relevance for people with MS; MBSR course delivery; and thinking about when might be the best time for someone with MS to take the course (Figure 7.5)

Figure 7.5 Theme 4 '*Improving the MBSR course for people with MS*'



7.5.4.1 Being better prepared

From the participant and instructors interviews there was a general consensus that any future course should be more disability-friendly. For the instructors, thoughts focused on practical considerations such as knowing more about who was coming on the course, having skilled nursing help on hand for more disabled course participants, having tea and coffee brought to the room and not left on a trolley, having the pre-course orientation session re-introduced, and having the necessary materials in place so that the home practices were available for a wider range of ability levels.

Participant views echoed this, suggesting a more accessible room such as that used from the second week onwards, and that people should be made more aware what would be required of them, both in terms of attendance and home practice. One participant who specialised in skills training through his job in human resources suggested making participant testimonials available to add credibility, and also suggested the use of visual aids in course delivery.

One difference between the instructors and participants was that the latter expressed a desire for more time to be made available for getting to know the other course participants, as this was a valued part of their experience.

In this context, it was also highlighted that the tea/coffee-break experience needed careful forethought in relation to the more disabled. One participant pointed out the difficulty fetching a hot drink from a trolley for someone like herself, dependent on elbow crutches. She also highlighted that mingling might also be difficult for those more disabled:

> *'I felt more disabled because I couldn't go and just grab a biscuit and grab a cup of tea. I felt more disabled because I had to ask other people.. ..It's easy to forget that this can also impact on the ability to socialise'* (**P6**)

7.5.4.2 Making MBSR more relevant to people with MS

Neither instructor felt that a great deal should be changed with respect to the course content. They both iterated that they saw MBSR as being a well-honed generic approach. However, they did think a more cautious approach was warranted for some aspects of the content, such as the mindful walking practice, which they felt should be referred to as '*mindful locomotion*' and that there was some scope for making the practices more accessible:

> *'Cautious about the walking, very carefully framing that, adapting the mindful movement, making lots of choice, as the body scan, whether people are lying or sitting, so maybe on the one hand acknowledging that this is a shared illness, but on the other hand not being pulled down by it'* (**I1**)

One instructor felt that, ideally, it would be good to include a day retreat, but acknowledged the practical difficulties associated with this in an NHS setting.

One participant, who left after the first week, felt that the course had been '*cobbled together*'. A few (4/17) stated that they would like more in the way of MS-specific material and practices, such as the science behind the mindfulness approach, and how that relates to what is known about MS and stress. Another felt strongly that mindful walking should not be included unless it was tailored in some way to meet with different ability levels. She felt that course delivery needed to be more sensitive towards the needs of those with MS, by differentiating it from other conditions, and ideally, that any future course design should be informed by someone with MS who is familiar with the experience of being chronically unwell:

> '*I don't think you can have mixed abilities walking round and everybody happy.. ..I just felt the delivery needed to be a bit more sensitive to the needs of people with MS and MS is very different from chronic fatigue or any other thing like that.. It might have been better to have somebody who has actually been ill or not been well to have an input into the delivery on the course'* (**P6**)

7.5.4.3 Improving delivery strategies of MBSR for people with MS

Several participants (4/17) reported a dislike for the male voice that featured on some of the home practice CDs. One participant expanded on this by describing how she would prefer a softer, more gentle voice, with a couple of participants suggesting that familiarity with the instructor's voice on another home practice CD made it easier to work with:

> '*I think the voices of the ladies who were taking the course were really nice. They were quite kind of soothing and there's nothing wrong with the male voice, it's just a few people in the class said: "I don't really like that man's voice".'* (**P10**)

One participant stated that she felt that the course manual was not appropriate for people with MS, that it was kind of '*American*', and there was too much focus on

disability, rather than ability. Surprisingly, another participant described how she felt that the course manual was designed with another condition in mind (Stroke), which was of course not the case.

7.5.4.4 Timing: when is the best time to learn mindfulness if you have MS?

Participants held differing opinions about when might be the best time to learn mindfulness in the course of MS. Two commented that they wished they had been fitter before taking the course, in one case in relation to the mindful movement, and in the other relating to beliefs about certain yogic breath practices.

One participant felt that it might be too much for someone who had been newly diagnosed:

> '*Well.., not so soon after diagnosis.. .. I think one girl in particular because it was very raw, it brought a lot of raw emotions to her, the sensation thing she was quite upset by it'* (**P7**)

On the other hand, another individual iterated that she wished that she had been given the opportunity nearer the time of her diagnosis:

> 'W*hen I was diagnosed, I mean it hit me quite severely and it was overwhelming and from a personal experience there was so much going on in my life and at the time I was alone with two children and I just was frantic, the whole time thinking "How am I going to manage if this happens again, how am I going to deal with things?" and it helps you put things in perspective. It's not saying "Well that's not going to happen" but it's kind of making you think "Don't stress too much about that, just dwell on the here and the now and what you can do, and don't beat yourself up for things that you can't do", you know. It's taken a lot of pressure off me, I know that whatever could happen might happen, but I'm not as panicked about it as I was before'* (**P10**)

7.5.5 Application of the Normalisation Process Theory 'lens' to the qualitative analysis findings

Following completion of the qualitative analysis, emergent themes were subjected to a retrospective analysis under the theoretical 'lens' of NPT (Table 7.3 and Table 7.4). This was used as an implementation guide, and no attempt was made to 'shoehorn' themes to fit the theory. Table 7.3 outlines how the emergent themes relate to the NPT constructs and Table 7.4 illustrates the 'NPT matrix' for MBSR.

Table 7.3 Mapping the emergent themes to the NPT constructs

Theme	NPT construct
1. Coming together for the course	
- Pre-course expectations	**Coherence**
- Being prepared and getting there	**Cognitive participation**
- Course context; getting it right	**Collective action**
- Becoming a group	**Collective action**
2. Doing the work of mindfulness	
- Coming face-to-face with MS: senses, sensations, and disability	**Cognitive participation**
- Making sense of MBSR group practices	**Collective action**
- Making sense of MBSR self practices	**Cognitive participation**
- Staying present, or dropping out	**Cognitive participation**
3. Getting it, or not	
- Being in the zone	**Coherence**
- Perceived effects from MBSR	**Reflexive monitoring**
- Relating to one's self	**Collective action**
- Relating to others	**Cognitive participation**
4. Improving the MBSR course for people with MS	
- Being better prepared	**Reflexive monitoring**
- Making MBSR more relevant to people with MS	**Reflexive monitoring**
- Improving the delivery of MBSR for people with MS	**Reflexive monitoring**
- Timing: when is best to learn MBSR if you have MS?	**Reflexive monitoring**

Table 7.4 NPT coding matrix for MBSR

1. Coherence	2. Cognitive participation	3. Collective action	4. Reflexive monitoring
a) Differentiation Is there a clear understanding of how the MBSR course differs from existing practice?	**a) Initiation** Are key individuals willing to drive the implementation?	**a) Interactional workability** Does the MBSR course make people's work easier?	**a) Systematisation** How are benefits or problems identified or measured?
b) Communal specification Do individuals have a shared understanding of the aims, objectives and expected benefits of the MBSR course?	**b) Enrolment** Do individuals "buy into" the idea of the MBSR course?	**b) Relational integration** Do individuals have confidence in the MBSR course?	**b) Communal appraisal** How do groups (patients/ clinicians/ managers/ MBSR instructors) judge the value of the MBSR course?
c) Individual specification Do individuals have a clear understanding of their specific tasks and responsibilities in the implementation of the MBSR service?	**c) Legitimation** Do individuals believe it is right for them to be involved?	**c) Skill-set workability** How does the MBSR course affect roles and responsibilities/ training needs?	**c) Individual appraisal** How do individuals appraise the effects on them and their work environment?
d) Internalisation Do individuals understand the value, benefits and importance of the MBSR course?	**d) Activation** Can individuals sustain involvement with the MBSR course?	**d) Contextual integration** Is there organisational support for the MBSR course? Are there contextual issues that matter?	**d) Reconfiguration** Do individuals try to alter the MBSR course? How do individuals think MBSR needs altered to meet the needs of those with MS?

7.5.5.1 Coherence – making sense of the course

Coherence is about how stakeholders make sense of a complex intervention [206].

Findings from the qualitative analysis demonstrated that most of the course participants interviewed (13/17) were new to MBSR. In terms of how participants felt MBSR differed from other approaches for managing their condition, the qualitative findings suggest that MBSR was perceived as different from what most people had previously experienced. For some, this difference may have acted as a barrier to participation and engagement. Better pre-course preparation could have helped participants have a clearer idea of what to expect, and possibly also how best to engage with the experience. In the case of the instructors, there was an idea that MBSR could facilitate less focus on the MS-identity, something that they perceived as prevalent and problematic in the condition. They assumed that lessening this focus would be good for participants. Some participants were invested in the hope that MBSR might offer them some relief from their symptoms of stress, pain, or difficulty sleeping, and this might facilitate taking part in MBSR, given the high prevalence of such distressing symptoms in people with MS. Thus, expectations differed between the instructors and participants, in part due to the lack of the usual orientation session, which had been dropped due to anticipated increased costs associated with its inclusion. Lack of an orientation session was particularly emphasised by the MBSR instructors as contributing to initial difficulties with the course, and possibly the attrition seen thereafter. The instructors saw this as relating to not having the opportunity to address expectations at an early stage. The instructors considered that their role was to deliver an otherwise standard MBSR course, without specific repose to MS; on the other hand, participants expected that the course would be more MS-specific. This mismatch in expectations could act as a potential barrier to future courses.

Also relevant here is home-practice and the important role it seemed to play in helping people ‘get’ the practices and the benefits of MBSR. More emphasis on the importance of the home-practices, and the personal responsibility involved in maintaining them from an early stage, might act as a potent facilitator to achieving the benefits (‘success’) and engagement with the MBSR course.

Proponents of mindfulness have repeatedly underlined the importance of MBI instructors' having their own dedicated practice [13, 153]. Interview feedback from participants suggested this emphasis was evident in this course too, where they relayed how the instructors were adamant about the importance of maintaining their own practice and how it had helped them. This may have helped participants to make sense of the benefits, value and importance of the practices, but others also pointed out that more could perhaps be done to communicate this point, including personal testaments from previous course completers, and inclusion of the aforementioned orientation session in future courses. See Box 7.3 for key message and recommendation regarding Coherence:

Box 7.3 Coherence – key message and recommendation

Key message: Expectations between participants and MBSR instructors were mismatched. Participants did not really know what to expect, and both they and the MBSR instructors had to 'catch-up' in this regard during the course. For some participants this was disappointing and is likely to have hindered their engagement.
Key Recommendation: A pre-course MBSR orientation session seems essential in order to manage participant expectations

7.5.5.2 Cognitive participation

Cognitive participation refers to the relational work that stakeholders undertook to create and sustain a community of practice around the intervention [206], for example that between the participants and instructors, but also, more broadly, where participants had to engage with other people in their lives, for example to help arrange child care, or transportation for coming to the course.

'Buying in' to the idea of MBSR does not appear to have been a problem for the initial recruitment target of 50 people, with 100% being recruited within the three-month timescale, which is notable given that most trials of complex interventions fail

to meet their recruitment targets [216]. The instructors had a pre-existing rationale for how they thought MBSR would help people in general, and those with MS specifically, by softening the MS-identity, and by changing the way individuals related to their experiences, including distressing embodiment sensations. Many participants appear to have accepted these ideas as well, reflected perhaps by increased mindfulness and self-compassion scores in the RCT findings, and by the qualitative findings, where some considered themselves more 'mindful' and compassionate in their daily lives. However, others did not. It is interesting to speculate if those dropping out early on might have 'bought in' had the environment been more suitable, i.e. with more exposure to the techniques, or if the initial dynamics of the group and/or setting had been different. In any event, it highlights again the importance of managing expectations appropriately in advance of the intervention.

There were several participants who dropped-out from the MBSR course (n=8). Reasons and timing varied. From those who attended any classes (n=21), some clearly did not feel it was right for them to be involved, with the mindfulness approach being perceived as counter-intuitive to at least three participants. Lack of an orientation session and/or a failure to identify and manage divergent expectations during recruitment may account for these discrepancies. However, most recognised that stress was a problematic area in their lives, including those who stopped attending, and many were keen to learn new ways of dealing with this issue.

Of those interviewed, the majority (n=10/17) were able to sustain mindfulness practice in some way, and in this regard the availability of a drop-in session could act as a facilitator for many to keep up the practices beyond the eight-weeks of the course. However, treatment adherence was sub-optimal, and participant feedback suggested that perhaps the most important factor in this regard related to managing pre-course expectations. Similarly, other participant feedback suggested strategic alterations to class, practice, and course duration might each act to facilitate and sustain broader engagement and adherence. See Box 7.4 for key message for Cognitive participation:

Box 7.4 Cognitive participation – key message and recommendation

Key message: Doing the mindfulness practices (treatment adherence) without a clear understanding of why they are being done, how they should be done, and why continued practice is required to see the benefits seems to be an important barrier to engagement and sustained involvement, especially in the early stages of the course. This may be even more strongly the case in those who have high levels of disability and comorbidity, or a strong illness identity.
Key recommendation: The environment for an MBSR course for people with MS has to be right**.** Disability and/or comorbid conditions can act as barriers to participation in MBSR. When catering for disabled/multimorbid groups this should be anticipated, and practices tailored to meet the specific needs of each individual, and the group.

7.5.5.3 Collective action

Collective action is about the operational work that stakeholders have to do in order to enact the practices of the new intervention [206].

Many participants described deriving benefit from the MBSR practices, and being able to integrate the techniques to meet various challenges in their daily lives. However, an obvious obstacle highlighted was the impact of disability on being able to participate in the practices. The course instructors described assumptions they held about how mindfulness might help people with MS, and to some extent these correlate with qualitative participant feedback about how the practices were used to deal with stress, how they related to themselves, and how they related to others. Similarly, quantitative findings from the RCT, such as enhanced mindfulness and self-compassion, further support this hypothesis.

Most participants reported benefit from the MBSR course, suggesting they had confidence in its potential role to assist with stress management, but this was not unanimous. An important, yet subtle shift in responsibility for symptom management may be evident amongst participants. For example, several participants described a

change in how they related to the fluctuation in their symptoms attributed to MS, with a more reflective attitude emerging in some. Others reported recognising a need to relate to their self differently, by being more self-compassionate. Some described a recognition that they needed to make more time for the practices, but simply couldn't find it.

On a macro- level, it is difficult to say whether organisational support exists for a MBI for people with MS. To assess adequately such issues would require a broader range of stakeholder interviews, to include MS clinicians and NHS managers. Both of the instructors used their administrative and lunch time to take part in the course, and thus their participation was in addition to their usual NHS workloads. Both reported that this presented challenges. Informal feedback from the instructors suggested that organisational support was not uniform, and following a change in management both were wary that they might not be similarly supported to take part in any future study. See Box 7.5 for key message from Collective action.

Box 7.5 Collective action – key message and recommendation

Key message: In order to get the benefit from MBSR, people have to do the practices. This relies on coherence and cognitive participation, where participants understand the importance of doing the practices, and 'buying in'. Generic MBSR courses/materials may not be optimal for people with comorbid conditions/disabilities. Practising in the context of chronic pain, limited fitness, and impaired mobility may not be practicable, or safe. Wide stakeholder involvement is crucial in making preparations for a disabled group.
Key recommendation: Enacting the MBSR practices relies on wide stakeholder engagement, understanding, and 'buying-in'. Judicious planning could help overcome operational barriers to participation amongst more disabled groups.

7.5.5.4 Reflexive monitoring

Reflexive monitoring refers to on-going appraisal and assessment of how the new practices of the intervention impact on the stakeholders and those around them [206].

The majority of participants who completed the course described using the MBSR practices in their daily lives in some form, with most describing benefit, feeling better, and being less stressed. Many described noticing beneficial changes in their relationships with others. However, two participants felt that attending a single class had been to their detriment. Nine out of 25 did not complete the course.

The standard clinical governance practice of the MBSR instructors i.e. to phone course dropouts to check on their reasons for non-attendance allowed insight into some important aspects of non-attendance relating to course organisation, structure, perceived focus, and content. In addition, the collection of 'informal' participant feedback during the course, and then 'formally' in written format at course completion allowed the MBSR instructors to enhance intervention fidelity, and to act reflexively to address the multiple difficulties that were highlighted in the first week of the course. Such feedback proved to be useful in making logistical alterations to the course i.e. organisation, setting, content etc, generating useful insights into how the course could be optimally reconfigured in light of the high levels of physical disability. The process of formal written feedback from participants at course completion allowed the instructors to gain insight into the value of the practices to participants, and to judge where these could/should be improved or modified.

As most participants were not normally patients at the NHS CIC, no formal arrangements were in place for 'follow-up'. Under normal circumstances, patients attending a mindfulness course there would follow-up with their usual Integrative Care provider at the centre, where issues arising from the course could be brought to light and addressed. The instructors highlighted the lack of such feedback as problematic for them, raising an important question about continuity of care for course completers, who might not want to attend the drop-in sessions, or have access to anyone else suitably qualified/au fait with the MBSR approach and its place in the 'bigger picture' of managing MS.

Participants had various suggestions for improving the course. Suggested changes related to course design, such as inclusion of an introductory day; smaller class sizes; shorter classes and practices; more time spent socialising with other course participants; using a more accessible room; excluding mindful walking; and making

the course manual more MS-specific and ability-appropriate. See Box 7.6 below for key message and recommendation regarding Reflexive monitoring.

Box 7.6 Reflexive monitoring – key message and recommendation

Key message: Routine safety and governance measures are important for MBSR courses, including suitable class space, embedded continuity of care, and standard follow-up procedures. Such measures assist in the ongoing monitoring of intervention fidelity. Applying course material flexibly, in response to participant feedback seems necessary, especially so in a highly disabled/multimorbid group.
Key recommendation: Generic MBSR courses are not suitable for everyone with MS. People who are highly disabled and/or multimorbid will likely need course organisation, structure, perceived focus, and content tailored to meet their specific needs. Changes to the generic course should be evidence-informed, monitored, and recorded. MBSR instructors may need additional training to deal with specialist groups, such as people with MS.

7.6 Discussion

7.6.1 Summary of key findings

This chapter has examined qualitative feedback from participants and instructors on their experiences of using MBSR as a treatment strategy for people with MS. Through using a rigorous qualitative approach to analysis, emergent themes relating to accessibility and acceptability of the intervention have been identified and organised. Mapping these onto NPT allowed key issues to be conceptualised around expectations, engagement and sustainability, around practical considerations relating to course delivery, and regarding how the course may need to be reconfigured to meet better the needs of those with MS.

The four main emergent themes to come from this analysis were:

1) ‘Coming together for the course – everyone has MS’
2) ‘Doing the work of mindfulness’
3) ‘Getting it, or not’
4) ‘Improving the MBSR course for people with MS’

Bringing together a group of people with MS with varied ability levels for a MBSR course requires careful forethought and preparation. People need to know what they are signing up to and what will be expected of them. Agreeing to take part in an eight-week course is a considerable undertaking for anyone, and likely more so when disabled. The venue for such a course should be disability-friendly.

Facing up to MS with a mindful and compassionate approach may have many benefits. However, turning attention to the areas of one’s body that are chronically in pain, or don’t work as well as they might otherwise, can be unpleasant for people, and these practices need to be couched carefully, in terms of language and connotation. Making sense of one’s experience of MS in a MBSR group could help some people, especially when being led through the practice by experienced instructors. Building upon such experiences with appropriate and accessible home practice materials seems to help some people with MS make a shift in attitude towards themselves, becoming more mindful and self-compassionate. In many cases, this beneficial effect may carry over into relationships with others, who can be important sources of social support.

Seeing positive effects from taking part appears to be important for people with MS, in order to ‘buy in’ to the practices, and may act to sustain involvement. The majority of participants in this study (13/17) reported beneficial effects from MBSR, but others did not, and this mostly seems to come down to a mismatch between pre-course expectations and the focus of the generic MBSR course.

These findings are further augmented by suggestions for improvement to the MBSR course. For example, a pre-course orientation session seems to be necessary, something which participants and instructors alike would value. There is perhaps scope also for tailoring the course content and delivery to make it more MS-specific, and bolstering teaching strategies to encompass a broad range of disabilities seems

sensible. At present, it remains unclear as to when might be the best time for people with MS to learn MBSR; in this study it was suggested by participants that times of high stress, such as around the initial diagnosis, or during a relapse are where having the MBSR skills on hand could be particularly helpful.

These themes emerged during a thematic analysis of participant and instructor feedback. This methodology has protected the originality of the data, rendering it both reliable and valid for people with MS. Further, these emergent themes have been scrutinised with regards to implementability of MBSR, under the theory-driven 'lens' of NPT. Using an established theoretical framework has the advantage of allowing the researcher to link findings with well-validated models of knowledge, thus enhancing generalisability [325]. NPT in particular is designed for assessing implementation issues in complex interventions [215], and has allowed a closer evaluation of potential facilitators and barriers to successful implementation of MBSR in this population, as well as helping in the process of considering how best to optimise the intervention. This conceptualisation has helped identify four key issues and recommendations for anyone contemplating MBSR for people with MS:

1) A pre-course MBSR orientation session seems essential for *coherence*, in order to manage participant expectations.
2) In the case of *collective action*, the environment for a MBSR course for people with MS has to be right**.** Disability and/or comorbid conditions can act as barriers to participation in MBSR. When catering for disabled/ multimorbid groups this should be anticipated, and practices tailored to meet the specific needs of each individual, and the group.
3) Regarding *cognitive participation*, enacting the MBSR practices relies on wide stakeholder engagement, understanding, and 'buy-in'. Operational barriers to participation could be overcome by judicious planning when dealing with highly disabled groups.
4) Lastly, when considering *reflexive monitoring*, MBSR courses are not suitable for everyone. People who are highly disabled and/or multimorbid will likely need the course organisation, structure, perceived focus, and content modified to meet their specific needs. Changes to the generic course should be based on empirical evidence and experience, monitored

and recorded. MBSR instructors may need additional training to deal with specialist groups, such as people with MS

7.6.2 Relationship to published literature

7.6.2.1 Emergent themes

There are very few published research studies that report on qualitative findings about how people with MS find taking part in MBIs [296, 313]. In the case of Hankin [296], the data in this study relies upon informal, and un-systematically collected views from MS patients and their partners on the impact of MBSR training, limiting its relevance to the findings from this current study. In the only other qualitative study on the use of MBIs in MS, Bogosian et al. [313] provided a more detailed analysis of participant experiences (n=15) of a remote-delivered Skype MBCT intervention for people with progressive MS. The researchers were interested in examining the potential mediating roles of several theoretical variables thought to be important in MBI mechanisms. These included acceptance and experiential avoidance, the ability to decentre from one's thoughts i.e. to see them as simply thoughts and not necessarily a reflection of reality, having compassion towards one's self, and self-efficacy [313] i.e. belief in one's ability to succeed in a particular situation/achieve a set task [326].

In terms of potential mechanisms by which MBCT might lead to reduced psychological distress, Bogosian et al. [313] reported supportive qualitative findings for all of their deductive themes, but a concurrent quantitative analysis of these putative mediator variables suggested that they only partially explained how the intervention acted to reduce psychological distress. As in this current study, Bogosian et al. [313] reported that participants found staying with distressing thoughts and emotions difficult, but that those who persisted derived benefit, describing the mindfulness techniques as useful tools for managing, and coming to terms with MS. They also found that the mindfulness practices helped participants experience pain in a new and more beneficial way, and to recognise and prise apart automatic cycles in their emotions. In keeping with findings in this current study, Bogosian et al. [313] reported that course participants became more aware of tendencies for self-criticism, and gradually became more compassionate towards themselves as the course

progressed. Bogosian et al. [313] also reported that the mindfulness practices helped participants feel more calm, and more in control.

In comparison with the emergent themes reported in this current study, Bogosian et al. [313] described the following inductive themes 1) Group dynamics, where being part of a regular group and everyone having progressive MS was seen as helpful by some participants, but not all. For example, hearing other MS patients' perspectives was helpful, but seeing more disabled individuals was at times challenging; 2) How participant pre-course expectations and worldview impacted on their experience of the course – one individual reported being open to 'Eastern philosophy'; whilst another saw herself as more pragmatic, and not really at ease with 'self-help' approaches [313].

Aside from MS, MBIs have been quite widely reviewed in the qualitative literature amongst people with other LTCs, where reports mainly focus on their impact on mental health. The largest of these has been a meta-synthesis of 15 empirical studies, where Wyatt et al. [320] reviewed MBIs for people with mental health difficulties. Their thematic synthesis included a variety of MBIs (two using MBSR). They generated quite similar themes to the current study, with eight higher order categories: 1) '*prior experiences and expectations*', 2) '*normalising and supportive process of the group*', 3) '*relating differently to thoughts and feelings*', 4) '*acceptance*', 5) '*a sense of control and choice'*, 6) '*relationship with self and others*', 7) '*struggles*', and 8) '*awareness*'.

In another qualitative review, Malpass et al. [327] used meta-ethnography to assess the literature in this area, collating data from 14 studies to assess how patients with chronic illness experience the mindfulness process. This included both mental health i.e. recurrent depression, and physical health conditions, such as pain, cancer, HIV, Parkinson's Disease, and patients undergoing cardiac rehabilitation. They arrived at three broad categories of how people make sense of the eight-week course, namely 1) a period of exposure to maladaptive strategies; '*perceived safe certainties*' where people learn about their usual, unhelpful ways of responding; 2) a period of learning new skills to cope; '*safe uncertainty*' where seemingly counterintuitive skills are being learned and things may seem more difficult; 3) transformation of the illness

experience; '*growing down*' which demarked a phase of becoming more expert in their own experience, associated with an increased sense of agency and self-efficacy. Some of the sub-themes were similar to the findings of this current study, with self-control/regulation, acceptance, embodiment, and response flexibility featuring amongst them. Another, smaller meta-synthesis including seven qualitative studies looked at experiences of mindfulness training amongst people with stress, anxiety, recurrent depression, Parkinson's Disease, or those taking part in cardiac rehabilitation [328]. The study examined how MBCT facilitates positive change, and again generated comparable themes to this current study: 1) '*taking control through understanding'*, 2)'*the impact of the group*', 3) '*taking skills into everyday life*', 4) '*feelings towards the self*', and 5) '*the role of expectations*'.

Being part of the group was highly valued by participants in this study, a finding that resonates with Bogosian et al. [313] and other accounts in the qualitative literature of MBIs in other chronic illnesses [329]. It has been suggested that such provisions should be made more widely available in the NHS [62] and that clinicians should remain cognisant of the benefits associated with peer support and socialisation in chronic illness, such as MS [329]. Qualitative findings from the use of MBIs in MS and other LTCs suggest an element of peer support, de-stigmatisation, and normalisation of common illness experiences may expedite a process of acceptance [313, 320, 327]. Social support improves QOL, impacts on perceived illness severity, and has been described as highly important for people with MS, in terms of adapting to receiving the diagnosis and subsequent illness adjustment [21]. Such a forum can allow for concerns, fears, and worries to be addressed between individuals with the condition, across disability levels [62].

In this study, participants mainly reported benefits from taking part in MBSR and learning to be 'mindful', both in the group, and away from the course on their own. Sirois et al. [316] suggest that a variety of skills are likely required for stress management in those with chronic illness. This fits with qualitative findings about MBIs in chronic illness other than MS, suggesting that individuals accessing MBIs tend to use techniques in a '*mix and match*' type approach, away from the course in their daily lives [320], and that MBIs can facilitate a transformation in perspective on

both illness and the self. This may, however, depend upon the attainment of meta-cognitive awareness, a key construct in the theoretical mindfulness literature [327].

Some people did not benefit much from the MBSR course in this study. To a certain extent, there may be a process of *learning the language of mindfulness* that facilitates a more healthy view of and/or internal dialogue with/about the self, but this may be harder for some to adopt than others. Wyatt et al. [320] also describe something similar in their meta-synthesis, the so called '*biggest challenge*', where they relate this to difficulties in keeping up the practices, especially during challenging times, where they possibly matter most.

7.6.2.2 Implementation issues

It is clear from this current study that generic MBIs are not suitable for everyone with MS, and identifying early on who will likely benefit seems necessary. Grossman et al. [177] conducted personal intake interviews prior to their MBSR intervention, in order to identify '*realistic goals*' for taking part, and this may have contributed to the low attrition and high adherence in that study, although it should also be noted that the mean EDSS (disability) level in that study was less than in the current study (3.5 versus 4.5), signifying a much lesser degree of mobility impairment. None of the five other MBI studies for people with MS described provision of an orientation session [289, 290, 304-306], and attrition was higher in these studies than in Grossman et al. [177] (range 12.5% - 43%). Findings from this current study also highlight another important consideration i.e. that MBSR facilitators may require enhanced training and supervision for working with disease-specific, specialist groups, which resonates with good practice guidelines for clinical MBI use in the UK (http://www.mindfulnessteachersuk.org.uk/) and also with general safety considerations [155]. In this study the mean number of years of mindfulness teaching experience between the instructors was 7.5 years, compared with nine years in Grossman et al. [177]. In general, other MBI studies in people with MS have not clearly described level of teaching experience [289, 290, 304-306].

Previous MBIs for people with MS have either used a generic [177], or an adapted MBI, sometimes with justification [305], but more often without [289, 290, 304].

From the qualitative findings in this current study, it seems likely that tailoring of MBIs will be required to meet the complex needs of people with MS, and that stratification by level of disability should be considered. Bogosian et al. [305] recruited more disabled individuals (mean EDSS 6.5), with considerable mobility impairment, but excluded mindful-movement from their MBI. The positive treatment effects generated in the Bogosian et al. [305] trial, alongside good levels of class attendance suggest that the modified MBI was acceptable in this context, but the study also failed to show improvements in fatigue scores, perhaps as a result of removing the mindfulness practices based in physical activity. Physical activity in general is regarded as integral to MS neuro-rehabilitation [44], and even quite disabled individuals (EDSS >6.5) report QOL benefits from exercise [330], whilst meditative movement in particular has shown wide-ranging QOL benefits amongst people with other LTCs, such as those with breast cancer, diabetes, heart failure, low back pain, and schizophrenia [331]. Bogosian et al. [305] also used shortened meditation and home-practice exercises. Qualitative findings from this current study suggest that some participants would appreciate shorter meditation practices and this alteration might improve treatment adherence. After Bogosian et al. [305], this current study has included the most disabled individuals. Thus, participants' feedback regarding their experiences of mindful-movement will be important in any future tailoring of MBSR for disabled groups.

In previous MBI studies in people with MS, settings have varied from within participant's homes [289, 305], to university hospital locations [177, 290, 304], to local MS Society accommodations [306]. From reports of existing studies, it is not possible to determine how participants have experienced the range of settings, or which might be best, but findings from the current study support the view that a suitable setting is important, especially in the context of high levels of disability and comorbid conditions. In this current study, having the MBSR course in a NHS tertiary care centre, with experienced nursing staff on hand to help, proved to be beneficial, and allowed quick adaptation to difficulties encountered with running the course for more disabled participants.

7.6.3 Strengths and weaknesses

The findings from this study add important information to the qualitative research literature on the use of MBIs for people with MS, where there is very little data. Through adopting a rigorous thematic analysis, informed by the framework approach, which involved senior qualitative researchers throughout, the reported findings can be confidently taken to represent the views of people with MS attending the course, and the MBSR course instructors. The iterative nature of the qualitative analysis and the involvement of multiple researchers in coding can be seen to enhance the internal validity and reliability of the findings. Use of NPT as a theoretical 'lens' through which to view implementation issues is a distinct strength, allowing valuable insights into what additional work may be needed to improve stakeholder uptake and engagement with a MBI for people with MS. The sample of participants covered a range of socio-demographic variables and MS phenotypes, making the findings applicable to wider MS populations in the community. The inclusion of instructor interviews allowed a degree of data triangulation, a different perspective on how the course had gone, and how it might be improved. Use of NPT as a theoretically based implementation analysis tool has allowed the development of key recommendations going forward, in terms of how MBSR can be optimised to meet the needs of people with MS.

Limitations include the limited geographic and demographic spread of participants, most notable in terms of ethnicity, which was mainly White Scottish, and the fact that none of the interviewees had SPMS. Further, not all participants consented to being interviewed. Some who completed the course were unwilling, and others who dropped out were either unwilling, or un-contactable. Their input might have added substantially to the findings. However, interviews were relatively in-depth in nature, in that no stringent time constraints were imposed upon them. In the event, the average interview lasted 45 minutes.

7.7 Conclusions

Findings from this study support the view that future MBIs should be specifically tailored to meet the complex needs of people with MS. In principle, MBSR appears to be a useful treatment option, but participant expectations need to be fully addressed before coming on the course, and an orientation session/interview seems necessary. Course venues for MBSR amongst people with MS should be carefully selected, to reflect likely ability and comfort levels of those participating. Certain modifications may be necessary to the meditation practices in order to make them more accessible and acceptable to people with MS, such as starting with shorter meditations and building up to longer durations as the course progresses. Home practice is deemed important by instructors and participants alike, especially by those participants who derive benefit from the intervention, and should be strongly emphasised from the outset. This work has demonstrated the value of broad stakeholder input in judging how best to implement MBIs in this population.

Chapter 8 General discussion

8.1 Summary

The aims and objectives of this thesis were to:

1. Measure comorbidity in people with MS in Scotland by characterising the number and type of conditions compared with the general population.
2. Delineate the existing evidence for effectiveness of MBIs in people with MS by carrying out a systematic review.
3. Test the feasibility and effects of conducting a RCT of a MBI for people with MS, and clarify whether a future definitive trial is currently merited.
4. Explore the perceptions and views of people with MS participating in a MBI (MBSR)
5. Examine the potential barriers to and facilitators of implementing a MBI for people with MS

This final chapter summarises the key findings of the thesis, discusses future optimisation considerations, and introduces possible future research directions.

8.2 Key findings

8.2.1 Epidemiology of comorbidity in people with MS – Chapter 4

The study of a large and nationally representative cross-sectional primary care database demonstrated that physical and mental health comorbidity is extremely common in people with MS in Scotland. After adjusting for age, sex, and SES, people with MS were more than twice as likely to have multimorbidity of other conditions compared with controls. The odds of having constipation, visual impairment, pain, migraine, epilepsy, and IBS were all more likely in people with MS versus controls. As the number of other physical conditions increased in MS, so did the chance of having associated mental health comorbidity. Women with MS were significantly more likely than men with MS to have a comorbid mental health condition. Overall

there was a three-fold higher prevalence of anxiety and depression in people with MS compared with controls.

8.2.2 Systematic review of MBIs in MS – Chapter 5

The systematic review found preliminary evidence from three studies that MBIs may be effective in improving anxiety, depression, fatigue, chronic pain, balance and QOL in people with MS. However, there were major limitations in the quality of evidence for two out of the three published studies included in this review. There have been three additional MBI studies published since the systematic review was undertaken with results providing further evidence of effectiveness for improving anxiety [305, 306], depression [304-306], distress, [305, 306], fatigue [304], balance and co-ordination [304], QOL [304], as well as likely cost-effectiveness in people with progressive phenotypes [305]. However, despite these new additions to the literature, the quality, and thus weight of evidence supporting the use of MBIs in people with MS remains low (Chapter 5; Appendix D).

8.2.3 Phase-2 feasibility RCT – Chapter 6

A phase-2 RCT (n=50) was conducted to assess the acceptability, accessibility, feasibility, and likely effectiveness of MBSR in a future definitive trial. Recruitment was shown to be feasible, with the target of 50 patients being met inside the predefined recruitment period of three months. Outcome measure completion rates post-MBSR (90%) and at three-month follow-up (88%) were good. However, MBSR completion rates were less than optimal with only 60% of participants attending >50% of sessions in the current study, and were less favourable than those described in other studies of MBIs for people with MS that reported on this outcome (range 92-95%) [177, 305]. Home practice completion in this study (average of 32.5 minutes per day) was lower than the 45 minutes per day suggested to participants at course commencement.

At the completion of the MBSR course, large beneficial treatment effects were evident on the primary patient report outcome for perceived stress, but were generally very small for QOL (weighted EQ-5D-5L scores). Secondary patient report outcomes

revealed large beneficial effects on depression, positive affect, anxiety, and self-compassion.

End-point effect sizes for primary patient reported outcomes at three-months after the end of the MBSR course revealed small positive effects on the PSS-10, and generally very small effects on the EQ-5D-5L. Primary outcome sub-scale analysis at study end-point revealed a small beneficial effect on the stress resilience subscale of the PSS-10, and a small effect on the anxiety/depression subscale of EQ-5D-5L.

For secondary patient report outcomes at study end-point (three months post-MBSR), improvements with large effect sizes were evident for mindfulness, positive affect, anxiety, self-compassion, and prospective memory. However, at this point the previously noted large beneficial effects on depression immediately post-MBSR were no longer apparent.

8.2.4 Qualitative research findings – Chapter 7

Participant interview feedback emphasised that being part of a group of people with MS was a valued (n=17/17) and acceptable (n=16/17) experience for most. However, the setting for the course was a source of concern for some (n=6/17), especially in the context of high levels of disability, as an upstairs room was being used for the course, with limited lift access, and the set up of chairs in the room had not left space for wheelchair users. Part of learning mindfulness meant coming face-to-face with having MS, and a few participants found this challenging (n=2/17). Most people (n=13/17) were new to MBSR, and a lack of an orientation session may have contributed to difficulties participants' had in making sense of the practices. Course content was generally acceptable to the participants, although notable exceptions were evident where disability impeded participation, such as in mindful-walking. From those participants who initially found mindful walking difficult (n=6/17), those who persisted reported beneficial effects (n=5/17). Most people who completed the course felt less stressed (n=13/17), whilst others reported diminished pain (n=5/17), and improved walking (n=4/17). Other beneficial effects, that were not anticipated as patient report outcomes in the RCT, included improved relationships with one's self

(n=9/17), and similarly with others (n=10/17). Course completers (n=14/17) thought that MBSR could be improved by making the content more MS-specific.

8.3 Synthesis of key findings

The epidemiology study (Chapter 4) demonstrated increased prevalence rates for physical and mental health comorbidity in people with MS. The systematic review (Chapter 5) revealed limited evidence of beneficial effects from MBIs on some of these comorbid conditions, such as anxiety, depression, and pain. In the feasibility RCT, besides the large beneficial study end-point effects on anxiety and cognitive function, small beneficial effects were also evident for pain (ES 0.32; p=0.27) and bowel symptoms (ES 0.28; p=0.31).

With respect to the other prevalent comorbid physical conditions found on the cross-sectional primary care database analysis (Chapter 4), some supportive evidence exists for the use of MBIs in these conditions too. The impact of MBSR training on migraine remains to be definitively established, although two RCTs [332, 333] suggest feasibility and likely effectiveness, with improvements noted in migraine frequency, severity, and duration. In the case of IBS there is a larger evidence base, with a recent review suggesting '*strong level-2 evidence*' for effectiveness, based on the results of nine empirical studies, the majority of which have used internet-based MBI approaches [334]. For epilepsy, three RCTs support the use of MBIs, with beneficial effects noted on comorbid depression [335, 336] and anxiety [337], seizure frequency [337], memory [337] and QOL [335-337]. Thus, additional benefits from MBI training may be available to people with MS who also have these comorbid conditions, and this could be assessed in a future study (see section below on optimising MBSR for people with MS).

In this study, patient report outcome measures from the phase-2 RCT at end-point (three months post-MBSR) (Chapter 6) suggested that the strongest beneficial effects from MBSR were on mental health and cognitive function i.e. positive affect, anxiety, and prospective memory. Mindfulness and self-compassion also had large effects at this point. Taken together with the large beneficial effects seen on stress and depression at the immediate post-MBSR time-point, these findings may indicate an

important potential role for mindfulness in helping people with MS improve aspects of their cognition function and cope better with psychological distress.

In terms of potential mechanisms of action for MBIs in people with MS, being more mindful has been linked in a cross-sectional study (n=69) with better illness adjustment, and diminished anxiety and depression in people with MS [314]. Greater mindfulness in MS patients has also been shown in another cross-sectional study (n=119) to be associated with lower stress, improved coping, and greater wellbeing [200]. A further cross-sectional study in people with MS (n=95) showed that being more mindful was correlated with higher QOL; an effect which appeared to be mediated by an improved ability to regulate emotions, and moderated by pre-existing depression [199]. However, cross-sectional studies such as these are limited, in that their findings cannot be used to infer causality. High quality longitudinal research is required to understand more clearly the potential mechanisms of action of MBIs in people with MS.

Recently, in a pilot RCT (n=40 people with progressive MS), using a remote Skype-delivered MBCT intervention, Bogosian et al. [313] investigated the potential mediating effects of acceptance, decentring, self-compassion, and self-efficacy in improving psychological distress; i.e. examining what active role that these variables had in diminishing psychological distress. The intervention comprised MBCT minus mindful-movement, with the course materials and content adapted to progressive MS. The researchers reported the largest mediating effects of 31% for decentring i.e. being able to view ones thoughts as simply thoughts, and not facts. This was followed by a mediating effect from self-compassion of 11%, acceptance 11%, and self-efficacy 8%. All of the mediator variables in the model had supportive qualitative findings derived from deductive thematic analyses, but the (mostly) small changes observed for the mediator variables could not explain the large reductions seen in psychological distress in the linked quantitative study [305, 313]. This could be because the analyses in Bogosian et al. [313] did not directly assess for the potential mediating role(s) of other variables that have been shown in meta-analysis as important mediator variables for improved mental health from mindfulness training, such as cognitive and emotional reactivity (strong, consistent evidence), mindfulness, and repetitive negative thinking (both of which have moderate, consistent evidence) [338].

Elsewhere in the mindfulness literature, Garland et al. [147] have reported from a prospective observational study of people with chronic pain (n=339) that a greater level of dispositional mindfulness was significantly and positively associated with positive-reappraisal coping (where SLEs are re-interpreted as either benign, meaningful, or growth-promoting) and finding beneficial meaning in adverse events (such as periods of illness). Garland et al. [147] also reported that positive-reappraisal coping mediated the stress-reductive effects of MBSR; that is to say, positive-reappraisal coping had an active intermediary role in the effects of MBSR on stress reduction [339]. Kuyken et al. [197] found that greater levels of mindfulness and self-compassion mediated resilience against recurrent depression in MBCT, whilst Nyklicek and Kuijpers [315] also reported that higher levels of mindfulness mediated the stress-reducing effects of MBSR in healthy subjects.

In summary, the findings from this thesis suggest that certain comorbid conditions are very common in MS, and that MBIs have the potential to impact favourably on a number of these, such as anxiety, depression, fatigue, and pain. In the phase-2 RCT, MBSR training led to large initial reductions in stress, depression, and anxiety, as well as improvements in cognitive function. These beneficial effects coincided with improvements in mindfulness and self-compassion. Some of these beneficial changes were not sustained, which may be due to diminished practice once the course was completed. Overall, the evidence base for MBIs in people with MS remains limited, and more research is required. In the first instance, optimisation of MBSR could improve outcomes. For example, improvements in mental health outcomes might be rendered more stable by making MBSR drop-in sessions available post-course. Furthermore, relatively little is known about how MBIs work across the spectrum of people with MS, and more research is needed to clarify mechanisms of action. The sections below cover these themes in more detail.

8.4 Future directions – Optimising MBSR for people with MS

The MRC guidance [19] suggests that before proceeding to a phase-3 trial, a researcher should be confident that the intervention to be tested is fully optimised.

This is because making alterations during a definitive study can cause delays, increase costs, and confuse results. The MRC guidance [19] suggests developmental work, such as that outlined in this thesis, can pre-empt difficulties in a larger study, and thus save on costs.

Phase-3 trials are designed to assess the effectiveness and safety of an intervention, normally involving randomisation, and usually testing the treatment against an active comparator group, such as CBT or another clinical intervention, under strictly controlled trial conditions. A phase-3 trial should be appropriately powered to detect clinically meaningful effects, and will be larger in scale than a feasibility study, with sample size often being informed by the outcome measurements from the feasibility/pilot work. Important factors include the observed effect sizes demonstrated on the patient report measures and the attrition rates. For example, if n% drop out of the feasibility study, one can assume that a similar percentage may drop out in a definitive study, and thus the sample size for a definitive study may need to be adjusted to take this possibility into account, so that the study power remains intact if the same percentage of participants drop out.

In a phase-3 trial, a health-economic analysis will usually be important, examining all relevant aspects of health and social care utilisation and costs, such as care practitioner contacts in primary care, secondary care, care at home, and for equipment provision and prescribing costs. Involvement of a health economist is recommended [19]. As part of such an evaluation, EQ-5D-5L scores would be combined with length-of-life estimates, and Quality Adjusted Life Years (QALYs) derived, together with the costs of health care utilisation, contributing to an overall assessment of cost-effectiveness [340].

A phase-3 trial may also involve the intervention being delivered over multiple sites, which can be useful when considering reproducibility, but also means that more stringent measures should be in place to assess fidelity, such as direct observation and recording of session content and delivery [19, 178]. By the time of delivering a phase-3 trial, the intervention to be used should ideally be in its final form, i.e. optimised, with no further modifications anticipated.

Campbell et al. [216] suggest that researchers should clearly define the problem and context, before setting out to optimise a complex intervention and its outcome assessment. The section below discusses suggested modifications to the MBSR intervention, with associated justifications from the thesis findings.

8.4.1 Improving attendance

The qualitative findings reported in this thesis (Chapter 7) suggest that the inclusion of a pre-course orientation session could improve engagement and uptake of MBSR, and by judicious management of participant expectations, potentially improve treatment adherence. Not knowing what the MBSR course involved, and the level of commitment required meant that some people who were recruited dropped out from class attendance early on. They were expecting more focus on MS (n=3/17), a positive psychology approach (n=2/17), more physical exercise (n=1/17), or one-to-one treatment (n=1/17).

Reasons for non-attendance at the individual MBSR sessions included difficulties with getting-up on time, arranging transport, arranging childcare, inter-current illness, work commitments, or holidaying. All of these issues could potentially be addressed, were the course materials made available online, or if the individual could remotely join the group i.e. via Skype. Tailored online MBCT has shown good levels of session attendance in epilepsy [335]; whilst a tailored Skype MBCT class was well attended in people with progressive MS [305]. However, such approaches using MBSR would need to be developed and piloted, before proceeding to a definitive phase-3 trial.

8.4.2 MS-specific materials

From participant interviews in this study, it seems that the MBSR course might have been better received had it been more MS-specific (n=6/17), and if the content had been made more disability friendly (n=6/17). Some participants (n=4/17) suggested course jargon should be minimised and carefully thought out, for example: '*exercise'* should not be used interchangeably with '*practice'* when describing the meditation practices, as this might make more disabled individuals feel excluded and unable to

participate. Furthermore, mindful-movement may also require careful consideration, with mindful-walking being re-branded as '*mindful-locomotion*'.

8.4.3 Mindful-movement and disability

Qualitative feedback from the RCT participants suggested that some of the standard MBSR practices, such as mindful-movement, were less accessible to more disabled individuals, where a sense of disability was accentuated (n=6/17). The optimum MBI movement strategy in MS is not known. Both Yoga and Tai Chi/Qi Gong have been used in previous MBI studies in MS [289, 290, 304], with studies that used the latter mostly recruiting less disabled individuals. The Hatha Yoga style postures typical to MBSR are relatively static in nature i.e. lying, seated, or standing, being held in a particular pose for a period of seconds to minutes [13], whilst Tai Chi forms are usually a more dynamic, flowing set of movements, most often performed in a standing posture [341]. Prescribing physical activities to disabled individuals seems desirable [330], but is a complex skill, especially as disability level increases [342], and involvement of a specialist physiotherapist in the design of future MBI movement practices for a range of ability levels could help. Both Yoga [343] and Tai Chi [344] can be adapted for more disabled participants, but more research is needed to assess which approach is best in MS across the spectrum of disability levels. For the next phase of study of MBSR for people with MS, having a range of Hatha Yoga postures on hand to recommend, in either a lying, seated, or standing position, makes sense. Any new movement practices could be piloted in a future study, prior to proceeding to a definitive phase-3 trial.

8.4.4 Shortened practices

A few participants (n=3/17) suggested that the duration of the meditation practices should be shortened, particularly at home. Optimum MBI session/ practice times have yet to be established [308], but shorter practices have been successfully used in other MBI studies in more disabled individuals with MS [305]. One approach may be to start all practices in a brief format, lengthening them depending on the ability of the individual. In the RCT, both pain (n=3/17) and fatigue (n=1/17) were reported as

problematic in terms of completing the practices; both are common in MS (Chapter 4; [277]) and potential barriers to participation.

8.4.5 'Booster' sessions

Several participants (n=7/17) in this current study found it hard to keep-up the practices once the MBSR course had completed. This could potentially account for the loss in treatment effects on stress and depression at three-month follow-up. The provision of regular booster sessions may help; such measures have been shown to help sustain beneficial treatment effects from MBCT in people with recurrent depression for up to two years post-intervention [318].

8.4.6 Outcome measurements

Effective mental health treatments in MS are limited, especially so for anxiety [10]. Findings from the comorbidity study (Chapter 4) confirmed that anxiety and depression are particularly prevalent in people with MS, and the systematic review (Chapter 5), and subsequent literature developments (Appendix D), together with the RCT findings (Chapter 6), suggest likely effectiveness of MBIs at treating these comorbidities in people with MS. Further, qualitative findings (Chapter 7) suggested reduced stress, and enhanced quality of relationships with self and others from learning to be mindful. In light of these collective findings, making a mental health measure a primary outcome in future studies appears justified.

Determining psychiatric 'case-ness' [345] may be of additional benefit in a future study, given that those patients with MS with case-ness for psychological distress, anxiety, depression, and fatigue appear to benefit most from mindfulness training [177, 305]. The Mental Health Inventory-18 (MHI-18) was used in this current study as part of the Multiple Sclerosis Quality of Life Inventory (MSQLI). MHI-18 missing values were generally low (0.3% at baseline to 12.1% at three-month follow-up), but the measure does not allow for estimation of psychiatric case-ness [346, 347]. Recent evidence-based guidelines [83] suggest that the best scale for detecting depression in MS patients is the Beck Depression Inventory (BDI) [348]; for general emotional disturbances, the General Health Questionnaire (GHQ) – both allow the assessment of

case-ness; and for emotional lability, the Centre for Neurologic Study - Emotional Lability Scale (CNS-ELS) [349] is suggested [83]. As a validated MS measure, the CNS-ELS would be a more suitable measure for assessing emotional lability in a future study.

In the RCT (Chapter 6), there were sustained beneficial effects on anxiety (ES 0.82) noted at study endpoint. No guideline recommendation is available for measuring anxiety in MS, although Fiest et al. [10] suggest that in such a scenario, evidence-based generic measures should be used. Once again, the MHI-18 subscale for anxiety does not allow for assessment of case-ness [346]. However, other generic scales do, such as the Hospital Anxiety and Depression Scale (HADS), which has been validated in MS [350], and used in prior MBI studies assessing the impact of mindfulness training on mental health [305]. Other generic measures that can determine case-ness include the Spielberger-Trait Anxiety Inventory (STAI) [351] (previously used to assess the impact of MBI training in MS - [177]); the Beck Anxiety Inventory (BAI) [352]; or the Generalised Anxiety Disorder-7 scale (GAD-7) [353].

From a physical perspective, comorbidities identified as prevalent in MS by the epidemiological study (Chapter 4) included functional bowel complaints (constipation and IBS), visual impairment, pain, migraine, and epilepsy. The MSQLI covers some of these conditions (bowel, vision, and pain), but not others (migraine and epilepsy). Outcome measures for migraine and epilepsy could be included in a future study, as could measures of co-ordination, standing and dynamic balance (shown to improve in other MBI studies in MS [289, 304]), and walking ability (as per improvements noted in qualitative accounts reported in Chapter 7). Table 8.1 provides a summary of suggested modifications to standard MBSR that have been discussed above.

Table 8.1 Optimising MBSR for people with MS

Modifications		Justification	Evidence source
1	Inclusion of a pre-course orientation session	Both MBSR teachers suggested such a move to convey the level of commitment required and help address pre-course expectations. At least 3/17 participants did not have an adequate understanding of what would be involved and dropped out after the first MBSR session	- Thesis Chapter 7, page 193
2	Consider development of online MBSR materials	Reasons for non-attendance of the MBSR sessions included difficulties with getting up on time, arranging transport, arranging childcare, inter-current illness, work commitments, or holidaying.	- Thesis Chapter 6, pages 139 - 140
3	Render course materials/ psycho-education MS-specific	Several participants (6/17) fed back that the generic MBSR materials were inaccessible, preferring instead a more direct link to be made between mindfulness practices and MS–related problems	- Thesis Chapter 7, page 202
4	Render the course 'jargon' disability-friendly	Some participants (4/17) felt that the language used to describe MBSR practices was insensitive towards MS and disability, such as 'mindful walking', or using the word 'exercise' instead of 'practice'	- Thesis Chapter 7, page 201
5	Make movement practices disability-friendly	Several of the more disabled participants (6/17) found certain movement practices accentuated a sense of disability. Both yoga and tai chi could be adapted to suit a range of ability levels.	- Thesis Chapter 7, page 188 - 189; - [343, 344]
6	Shorten some MBSR practices	Several participants stated a preference for shorter practices, particularly at home (3/17). Some (3/17) found sitting difficult due to pain; one person found fatigue limited the participation in the enquiry process.	- Thesis Chapter 7, page 190
7	Provide post-MBSR 'booster' sessions	Several participants (4/17) spoke about wishing to come to such sessions; two people cited practicing less after the course, as classes had finished. Such measures have been shown to sustain beneficial effects of MBCT for up to two years in people with recurrent depression	- Thesis - Chapter 7, page 192 - [318]
8	Make a mental health outcome a primary outcome measure; one which allows assessment of case-ness for anxiety and/or depression	Anxiety and depression are highly prevalent in MS. Effective treatments are limited. The RCT found sustained beneficial effects on anxiety. The largest effects found in other MBI studies in MS suggest that those with 'case-ness' benefit most. Recent evidence-based guidelines stipulate that the General Health Questionnaire (GHQ) and the Beck Depression Inventory (BDI) are the most suitable instruments in the MS population; for anxiety, generic measures can be used	- Thesis Chapter 4, page 90 - 91 - Thesis Chapter 6, page 141-146; - Appendix D. - [10, 83]
9	Measure the impact of MBSR on other prevalent MS comorbidities	The comorbidity study demonstrated an increased prevalence of constipation, migraine, epilepsy, and IBS – these areas were not explicitly included in the patient report outcomes, but have been shown elsewhere to improve with MBI training	- Thesis Chapter 4, page 91 - 93 - [334-336]
10	Include physical outcomes shown to benefit from MBIs in other MBI in MS studies	Mills and Allen [289] and Burschka et al. [304] demonstrated improved standing and dynamic balance, and co-ordination from training in mindfulness using Tai Chi	- Thesis Chapter 5, page 113; - Appendix D

8.5 Possible future research directions

8.5.1 Biologic outcome measures

There are now six published outcome studies, in addition to the trial in this thesis, that provide evidence on the use of MBIs in people with MS for reducing stress, improving mental health, QOL, and some aspects of physical health such as fatigue, pain, co-ordination, and balance [177, 289, 290, 304-306]. Added to these are three cross-sectional studies that suggest benefits to people with MS from being mindful [199, 200, 314], such as enhanced illness adjustment, improved QOL, coping, wellbeing, and emotional regulatory skills. There is only one longitudinal study that has assessed potential mechanisms of action [313]. All of these studies have focused on patient report outcomes (Appendix D), but no study has assessed any biological effects from taking part in MBI training.

It remains unclear from the existing literature how self-report effects from MBIs correlate with physical outcome measures. In the RCT (Chapter 6) training in mindfulness was associated with diminished stress and improved mental health, but there were also small beneficial sustained end-point effects (three months post-MBSR) noted for fatigue (ES 0.33; p=0.27), pain (ES 0.32; p=0.27), and bowel function (ES 0.28; p=0.31), suggesting some positive impact on physical symptoms. Whether these improvements resulted from improved mental health, or reflected improved underlying physical processes/ functioning remains unclear. Linking self-report outcomes with biological markers could provide further insight into how MBIs may work in this context.

Contemporary models of RRMS and, to a lesser extent, progressive MS phenotypes, propose that inflammation is a key mechanistic component of pathological disease activity. In this context, peripheral episodes of inflammation i.e. outwith the CNS, have the potential to contribute to relapses in RRMS [1, 20, 25, 29]. One potential cause of peripheral inflammation in people with MS is perceived stress [98]. Stress-related dysfunction in the neuroendocrine [303] and immune systems [94] are thought to be common problems in MS, and may also impact negatively on the risk of developing metabolic, and cardiopulmonary comorbidity in this group [263]. In the

general population, greater levels of perceived stress are associated with excess mortality [50]. A possible explanatory model for this in biologic terms is Allostatic Load (AL) [99]. AL reflects background inflammation and disordered homeostasis resulting from stress, all of which are problematic in MS [94]. AL measurements include those reflecting function in the neuroendocrine, immune, metabolic, and cardiopulmonary systems, alongside anthropometric recordings. A selection of such measures could be collected in future studies of MBSR for people with MS; for example to assess the impact of MBI training on autonomic nervous system activity i.e. heart rate variability, blood pressure, and pulse, and/or markers of peripheral inflammation, such as C-Reactive Protein (CRP), Tumour Necrosis Factor-Alpha (TNFα), and/or Interleukin-6 (IL-6) [302]. If MBI training decreased activity in the sympathetic nervous system (SNS) and/or reduced peripheral inflammation, then theoretically this could lead to diminished MS disease activity [98]. Collecting and processing such samples would require feasibility testing, prior to inclusion in a definitive trial of effectiveness, and the potential financial costs would need to be factored into consideration (Table 8.2).

Table 8.2 Possible Allostatic Load biomarkers [91]

System	Measure(s)
Neuroendocrine	Cortisol, Dehydroepiandrosterone, Adrenaline, Noradrenaline, Dopamine, Aldosterone, Prolactin, Insulin-like growth factor
Immune	C-reactive protein, Interleukin-6, Tumour necrosis factor-Alpha, Fibrinogen
Metabolic	Total cholesterol (TC), Low- and High-density lipoproteins, High density lipoprotein/TC ratio, Glycosolated haemoglobin, Glucose, Insulin, Albumin, Creatinine, Homocysteine
Cardiopulmonary	Blood pressure (systolic and diastolic), Heart rate, Pulse, Peak expiratory flow rate
Anthropometric	Hip-waist ratio, Body mass index

As discussed in Chapter 2, another approach that has been used to assess the biologic impact of CBT-based stress-reduction training in people with MS is Gadolinium-enhanced Magnetic Resonance Imaging (Gd+MRI) [7]. Measuring MS relapses based on participant-report measures risks recall- and subjectivity-bias; Gd+MRI lesions are a highly sensitive indicator of MS disease activity and can be used to predict relapse [116]. Building upon the findings from Mohr et al. [7], Gd+MRI scanning at regular

pre-defined intervals (i.e. baseline, then monthly until study endpoint) could be used in a future study to assess objectively the effectiveness of MBSR at reducing relapse rate (number of BBB lesions) and CNS disease burden (size and number of T2 lesions) in those receiving MBSR versus controls.

MRI has also been used to study neuroplastic effects associated with MBIs [354], including in other neurodegenerative conditions such as Parkinson's Disease [355], but not to date in MS. Such an approach, where the theoretical goal of MBI treatment lies in preserving brain reserve and/or enhancing cognitive function [356], could be studied using MRI to assess objective structural/ functional brain changes, such as improved connectivity/ adaptive cortical reorganisation. Such measures could be correlated with neuropsychological testing, may help in the development of much needed novel strategies for cognitive rehabilitation [357], and might add useful insights into putative MBI mechanisms of action.

MRI also has a role in the study of cognitive impairment in MS [357] where subjective and objective reports of impairment often differ. Both show only limited correlations with T1 lesions (reflecting demyelination and axonal density) and T2 lesions (MS pathology, such as inflammation, oedema, demyelination, axonal loss, gliosis, and re-myelination), but stronger associations with site-specific brain atrophy i.e. in the corpus callosum, or more widespread brain atrophy [357]. This current study found large improvements in prospective memory (ES 0.81; $p<0.05$); and non-smaller improvements in retrospective memory (ES 0.35; $p=0.35$), as well as planning (ES 0.31; $p=0.31$), and attention (ES 0.23; $p=0.40$) at end-point, three months post-MBSR (Chapter 6). Correlating such findings with objective MRI measures in a future study could help clarify potential mechanisms of action for mindfulness in this context, where associated cortical reorganisation, such as increased activation of the dlPFC may have important clinical implications i.e. maintaining memory function and processing speed in the face of declining neural reserve [357]. The financial costs associated with collecting and analysing MRI measures would require careful consideration.

8.6 How could the research in this thesis have been improved?

Reflecting upon the process and findings from this thesis, the next steps for this body of work require careful consideration. The rationale for carrying out further research in this area seems justified, in that stress is prevalent and problematic in people with MS, existing interventions appear to be limited in scope and effectiveness, and that MBSR appears to be acceptable to people with MS. However, a retrospective analysis highlights that important questions in this realm remain unanswered at this point, and these could potentially have been more fully addressed in this thesis, had different methods been selected to carry out the work and time allowed.

8.6.1 Was a RCT the right study design to use?

Firstly, it should be considered whether proceeding to a RCT at the feasibility testing stage was premature. An alternative option that was also considered was to work instead on optimising the intervention first. This could have involved a pre – post- observational study to test the feasibility of delivering MBSR, where recruitment, retention, treatment adherence and outcome measure completion could all be tested. Nested semi-structured interviews could have been carried out in a similar fashion post-intervention to inform acceptability and accessibility, along with barriers and facilitators to implementability. Following this, optimisation changes could have been tested in a second pre-post- observational study, where a modified MBSR course would be delivered. By following this alternative pathway to a logical conclusion, iterative changes could be made to successive courses and outcome measures up until no further changes were adjudged necessary. Thus, a series of several pre- post- studies could have been used, potentially with smaller group sizes, testing a wider range of outcome measures for feasibility, acceptability, and cost at each iteration, for example the recently developed Brief Inventory of Perceived Stress (BIPS) [358], or more invasive measures, such as salivary cortisol testing or blood sampling [302]. However, testing such measures would require prior approval by the Research Ethics Committee and host Health Board. The timescale allowed for data collection for the PhD limited this option, where the early phases of the work focused instead on

delineating the epidemiology of comorbidity in MS in Scotland and on undertaking the systematic review.

Collecting qualitative data between successive iterations of pre- post- MBSR groups could also have been advantageous. For example, such an approach could allow for successive modifications to be instituted following each course iteration, and thereafter assessed for feasibility, acceptability, and potential effectiveness in the subsequent iteration and so on. In this scenario, the qualitative data collected could be subject to rapid appraisal methods [359], whereby more pragmatic and expedient thematic analyses would be undertaken in a shorter timescale between successive MBSR courses, but this would have required a team of researchers, something which was not feasible within the constraints associated with the PhD. The benefit of this method is that each successive course could be optimised based on dynamic feedback from participants.

Reflection on the participant responses following standard MBSR outlined in this thesis suggests that the topic guide for the semi-structured interviews could be improved upon, so that a greater focus be placed upon the acceptability and accessibility of specific MBSR practices and the content of the psycho-educational material. For example, questions could ask in particular about participant experiences and preferences concerning the 'core' practices of mindful breath awareness, mindful body awareness, and mindful movement. Furthermore, issues raised in the interviews reported in this thesis may be homed-in on further, such as whether mindful-walking is better received by a subsequent group when branded differently as 'mindful locomotion', or whether adaptations put in place for more disabled individuals are well received, or not.

In terms of the NPT analysis, this could have been augmented by the inclusion of data from a broader range of stakeholders. This was considered at the time of protocol development, specifically where interviewing GPs, MS Clinicians and NHS Managers would have provided useful data that is absent in the current thesis, but important when considering the 'bigger picture', where potential factors that may influence the choice to support a new intervention such as MBSR, or not, could have been explored in greater depth. In keeping with national guidance on the management of MS in

primary and secondary care [44], the specialist MS service in the West of Scotland is a multidisciplinary agency including Neurologists, MS Specialist Nurses, Rehabilitation Medicine Consultants, Neuro-physiotherapists, Occupational Therapists, Neuropsychologists and other Allied Health Professionals. Interviews with MS clinicians could have explored current knowledge and understanding among such stakeholders of the potential role of MBIs in their clinical practice, where they think MBIs might fit, whether MBIs would be supported, or not, and why, and how best MBIs might be tailored to meet the complex needs across the spectrum of MS phenotypes and stages of disease progression. Interviewing such clinicians before testing MBSR could conceivably have fed into intervention design. However, due to the time and resource constraints associated with the PhD, extending the qualitative interviewing schedule to include these other stakeholders was not felt to be feasible.

8.6.2 Assessing health economic benefits from MBSR

The feasibility of carrying out a health economic evaluation was considered at the time of protocol development for the RCT reported in this thesis. However, practical time and resource constraints associated with the PhD were considered to render this option infeasible.

Evaluating the health economics of complex interventions may be challenging, both in terms of the complexity of the intervention, such as multiple potential active components, and of the system in which it is to be evaluated, which may be non-linear and largely self-organising, such as the NHS, or, as evident from the qualitative findings in this thesis, even extending out to the patient's family circle, and beyond. Similarly, deciding when to assess health economic benefit from a complex intervention is not necessarily a straightforward, or 'one-off', decision, and it is acknowledged in the empirical literature that the perceived 'value' attributed to an intervention is likely to increase substantially following successful implementation [360]. As an example to illustrate how this might apply in reference to the current thesis, as MBIs become more widely known about and used, a 'phase-shift' in perception, attitude towards, or against them may heavily influence economic benefits. In the case of MBSR for MS, this might mean that as MBSR becomes more widely known and/or accepted in the MS patient- and clinician- communities, then

more patients may seek to access the resource. As suggested by some of the qualitative findings in this thesis, having a mindful attitude towards previously distressing symptoms might influence how frequently patients seek healthcare provider advice/contact. This could conceivably have a spin-off effect on how MS patients use their GPs, the MS Specialist Nurses, or Consultant-led services.

In any event, a health economic evaluation is increasingly seen as necessary for novel complex interventions, given that most health care systems around the world are resource limited, and is frequently used in the decision making process as to whether to make a new intervention available in routine practice, or not [361, 362]. Furthermore, Shiell et al. [360] suggest that not knowing the active components of a complex intervention, such as group psychotherapy, should not serve as a deterrent to undertaking a health economic evaluation, as long as resource use ('inputs') can be clearly identified and benefits measured ('outputs'). The method is, however, necessarily limited, in that key aspects of the intervention, such as the skill of the individual MBSR instructor(s) (a 'resource'), the dynamic content of each individual group, or the overall group dynamic are not directly measured or included in the analysis. Instead, 'resource' focuses on session numbers, session lengths, group 'n', instructor salary costs, venue costs, and 'output' focuses on what effect MBSR has on health outcomes and health service usage.

A cost-effectiveness analysis is the most commonly used method of health economic evaluation, with a related alternative being a cost-utility analysis. Both measure the consequences of taking part in an intervention, versus not; in the former via practical units such as life years gained, or in the latter via preference-based health measures like quality- or disability-adjusted life years [361]. In the UK, NICE recommends the use of QALYs gained, as these standardised units allow for clinical benefits to be compared across conditions, whereby informed decisions can thus be made about how to prioritise access to clinical interventions [363].

The RCT wait-list control design used in this thesis would have allowed for an assessment of health economic benefits, as opposed to comparative-effectiveness, had an active comparator group instead been employed. Assessing health economic benefits could have scrutinised resource use by participants undertaking a MBSR

course versus controls. Bogosian et al. [305] used such an approach in a pilot study assessing the use of a SKYPE-delivered modified MBCT course against treatment as usual for people with progressive MS. They used the Client Service Receipt Inventory (CSRI), which measures 'formal' individual-level data relating to hospital, community, social care contacts, along with 'informal' care from friends and relatives [364]. They found that the modified MBCT training was associated with lower costs for both formal and informal care provision, using QALYs and distress scores on the GHQ as proxy measures. They reported no significant differences in QALYs between those receiving MBCT versus controls, which could be due to limitations of some aspects of the EQ-5D-5L, where physical/mobility issues are unlikely to improve in progressive phenotypes following mindfulness training.

The same issues with the EQ-5D-5L may apply in the current study, where improvements noted in the RCT were mainly on the anxiety/depression subscale, and were very small, or negligible on the other components. Kuspinar and Mayo [187] suggest that generic QOL measures such as the EQ-5D-5L miss a great deal of what matters most to people with MS. Rawlins suggests that a key scientific value judgement when assessing health economic benefits from a new intervention relate to whether or not QALYs have been appropriately assessed [363]. Newer measures, based on MS patient preferences, such as the Multiple Sclerosis Impact Scale-29 (MSIS-29) could offer a better alternative in a future study, with a focus on common MS difficulties such as grip strength, carrying things, balance problems, difficulties moving about indoors, clumsiness, stiffness, weakness, ataxia, spasticity, and temperature disturbances [365].

8.6.3 Patient and Public Involvement

Patient and public involvement (PPI) in health and social care policy is a UK Government priority, with the aim being for individuals who use health technologies being able to shape the services they use [366]. Taking into account service user views fits with aspirational democratic sociocultural values in the UK, such as accountability, citizenship, and transparency [367]. On a more practical level, one of the aims of the work carried out in this thesis was to identify whether or not standard MBSR would be acceptable and accessible to people with MS. Thus, greater PPI

could have potentially improved the quality and relevance of the findings in this thesis by providing unique advice and insight from PPI sources into the choice of intervention and how it should be delivered to a more disabled group, and potentially also into the methods used to assess effectiveness, such as whether stress and QOL should feature as primary outcomes, or not. Recent systematic review evidence suggests that PPI positively impacts on the quality and appropriateness of research, where user-focused research objectives can be identified, user-relevant research questions highlighted, user-friendly information, research packs and interview questions developed, along with improved recruitment strategies and methods for effective dissemination of findings [368].

In the UK, the national advisory group INVOLVE has created guidance for researchers regarding PPI with research. According to INVOLVE, PPI can mean public involvement in working with funding bodies to prioritise research, to sit on a research steering group, to contribute to the development of research materials, or to undertake interviews with research participants. INVOLVE suggest that PPI should ideally commence early in the research process, should involve multiple people with experience of the condition under question, so as to increase breadth and experience of the sample, although no clear guidance on an adequate 'n' is suggested [367]. At present there is no consensus in the literature as to what constitutes an adequate 'sample size' for proper PPI, but another recent systematic review focusing on PPI in the UK presented data from 28 studies, where participant numbers ranged from six patients in a primary care trust, to 167 people, including 78 lay members, in a nationwide study [366].

In this thesis, the RCT study protocol was subjected to prospective peer and lay review, including three patient members of the UK MS Society (Appendix A). Clearly, this small number of views cannot be said to be representative of the spectrum of people with MS who might wish to share views on the development of a bespoke MBSR course, nor can the consultation be described as dynamic, in that it was based on one-off responses to remote reading of the protocol. Other potential 'recruitment' streams for PPI suggested by INVOLVE that could be used in a future study for consultation and/or collaboration include advertising in local GP surgeries or hospital outpatient departments, by contacting local NHS Trust Patient Advice and

Liaison Services, by using the 'People in Research' website, via local TV, radio, or newspaper media outlets, through local voluntary sector services, or via the social media [367]. In this study, such methods were used to recruit participants into the RCT, but could also have been used in advance of the study to facilitate broader PPI in the research design stage going forward.

8.6.4 Was standard MBSR the right intervention?

In this thesis MBSR was chosen as the intervention for the exploratory RCT based on the limited information that had emerged via the systematic review on its prior use in people with MS. The study by Grossman et al. [177] had suggested that delivering MBSR was generally feasible under RCT conditions, and likely to be acceptable, accessible, and potentially effective in less disabled people with MS. However, the aforementioned study had been purely quantitative in nature, with no participant feedback reported. Thus, it was unclear whether there was evidence and/or scope for judicious tailoring based on participant experiences. Furthermore, the systematic review had identified a total dearth of information on this subject, with only Hankin [296] providing cursory snippets of qualitative data on how couples faced with a diagnosis of MS had found MBSR. The other quantitative studies identified in the systematic review were of low quality, having small sample sizes, and questionable research design. The information they contained could provide little further guidance on whether to use a standardised MBI, or not.

MBSR was designed to help reduce stress among people with LTCs. The only other standardised MBI that could have been chosen was MBCT. However, the focus of the thesis was on stress reduction, and although depression is common in people with MS, MBCT was specifically designed and manualised as a preventative treatment approach for recurrent depression. Thus, MBSR was felt to be the most appropriate.

In this study, feedback from MBSR participants suggested that standard MBSR is likely to need modification in order to improve its acceptability, accessibility, and relevance to people with MS. In terms of effectiveness and health economic benefit, whether modifications should be made prior to testing the intervention based on PPI, or from participants after receiving the standard version is a moot point [366].

Bogosian et al. opted for the former in their study using SKYPE-delivered MBCT, where a series of experimental case studies with patients with progressive MS were undertaken prior to proceeding to the RCT that piloted the adapted course. This led to shortening of the practices, the removal of mindful-movement, the adaptation of cognitive therapy exercises to explore how thoughts and feelings related to anxiety and low mood in MS, and the development of bespoke home practice CDs [305]. The obvious limitation of the former method is that one cannot know whether the standard MBCT course would have been more or less effective than the modified version.

What does seem clear, both from qualitative findings in this thesis and from the empirical literature [62], is that people with MS value effective stress management interventions, as well as clinicians' having knowledge about their condition. Thus, the development of a tailored stress management course makes sense. The optimisation changes suggested in this chapter may go some of the way to addressing this, such as removing practices like mindful walking, or simplifying mindful movement. However, how best to adapt the psycho-educational material is potentially more challenging.

Mohr has developed a CBT-based stress management intervention for people with MS, which makes clear for patients and therapists alike the links between stressful events, mental health, and MS relapse [369, 370]. As covered in Chapter 2, the empirical literature suggests that stress is detrimental in people with MS, in that it may increase the likelihood of developing mood disorders, diminish QOL, and possibly increase vulnerability to MS relapse. However, in the case of relapse, the data that exists is suggestive, but far from compelling. Furthermore, suggesting that stress may precipitate disease activity may actually be harmful to people with MS, in that they may feel responsible in some way for having the condition, and existing review literature on stress appraisal and coping in MS highlights that seeing the condition as having a psychological basis is associated with worse adjustment [3].

An alternative solution could be to tailor the MBSR teaching materials to common MS problems, without seeking to make the link between stress and disease activity until such times as this area is more fully understood. The findings from this current study could inform the development of such a protocol specifically for people with

MS. Such an endeavour could also involve multiple stakeholder/source input, from patients with MS, to MS clinicians, to the empirical literature. Such workbooks have been widely produced for CBT-type interventions for specific health conditions [371], and other examples exist for MBIs where interventions have started out using standardised protocols and adapted to suit the ecology of specific health conditions such as Mindfulness-Based Relapse Prevention (MBRP) [372, 373], and Mindfulness-Based Eating Awareness (MB-EAT) [374].

8.7 Conclusion

To conclude, physical and mental health comorbidity is common in MS and current treatments are limited in scope and efficacy. MBIs are a potential treatment option, but current limitations in the evidence base preclude definite conclusions as to their utility. MBSR appears to be feasible, acceptable, and accessible to people with MS, including those with quite significant levels of disability. MBSR is also potentially effective at reducing stress and improving mental health and cognitive function. However, less than maximal levels of treatment adherence and small effect sizes on primary patient report outcome measures at end-point assessment in a feasibility RCT suggests that further optimisation work is necessary before proceeding to a definitive phase-3 trial. Optimisation of MBSR could potentially improve uptake and sustain engagement, whilst outcome measure refinement could be tested via further piloting, prior to undertaking a definitive phase-3 trial. Use of the MRC guidance [19] has allowed a comprehensive and systematic approach for investigating this complex area and it will be useful to continue to use this approach for any future research on the use of MBIs for people with MS.

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Appendices

Appendix A - Patient and Public Involvement grant application to the UK Multiple Sclerosis Society. Lay reviewer feedback

Reviewer #1

Question: Q1. Please score relevance and importance this project might have for people with MS.

Answer: 5 - Very good

Question: Q2. If people with MS will be participants, please score how well the researchers have taken into account their needs.

Answer: 4 - Good

Question: Q3a. Please score how well the researchers have involved people with MS in the planning of this study.

Answer: 4 - Good

Question: Q3b. Please score how well the researchers have planned to involve people with MS during the study.

Answer: 4 - Good

Question: Q4. Did you find this lay summary easy to understand and well written?

Answer:

1. Relevance and importance.

The accumulative, debilitating effects of MS, and the nature of this chronic disease, results in higher rates of anxiety and depression than in other comparable long term health conditions. Thus, the aim of this project, to investigate whether mindfulness therapy is an effective tool for stress management in MS, is highly relevant and potentially very exciting should it prove successful. It may, by alleviating stress, reduce relapses and further degeneration of the myelin sheath. As there is some evidence to suggest that extreme stress can exacerbate disease activity, which was certainly the case for my daughter and of many young people I know as a committee member of two MS branches, any study which may result in stress management is very important.

MBSR was originally introduced to help people with chronic pain and then depression - commonly found in PaMS - and it is known that MBSR helps people with similar health problems to MS. However, research evidence which specifically investigates the effects of MBSR on MS is limited which this extensive feasibility study aims to address.

Currently, CBT is seen as the most successful psychological intervention but appears to be dependent on ongoing therapist contact which is especially difficult for those with transport problems, mobility issues and fatigue. MBSR not only operates differently to CBT, but also can be learned and then practiced at home without the need of a facilitator. This is especially important for PaMS who are not always well enough to attend classes and like anyone else, can not predict when a stressful situation might occur. The emphasis on self - practice, daily and weekly homework to embed mindfulness techniques may make this a long-lasting alternative to CBT. The extensive qualitative and quantitative data to be assessed in the investigation will hopefully provide concrete evidence as to why PaMS should receive this treatment. As it does not require long term intervention from course facilitators, it would also be cost-effective.

2. How well researchers have considered needs of PaMS.

Researchers have considered the needs of PaMS for most of the trial as far as I can tell although two and a half hour classes spread over a week for eight weeks could be onerous in terms of transport, access, and potential ill health. Additionally, using a broad inclusion EDDS scale of 1 to 7 might further exacerbate such issues. Weekly homework (specific form not included) and daily exercises to be carried out at home may also prove too ambitious for some participants. Although the classes would be based on relaxing Yoga techniques, the length and content of each class within the week and where it would take place were not included in this application. Without this information, it is more difficult to assess how well the researchers have considered the needs of PaMS.

Recruitment is more considerate as the feasibility study is open to interested, eligible individuals via their care providers. Getting in touch with the researcher is entirely up to the individual. Potential volunteers contact the researcher by phone, who will discuss the study, answer any questions, and arrange a mutually convenient time and venue in which to meet; helpful to people with MS who may have transport and mobility issues. Posting information is useful back-up especially as PaMS might struggle with concentration and memory. The researchers have explained exclusion criteria in depth which appears to be entirely logical.

Both participants and course facilitators evaluate the effects of the lessons. I particularly like the fact that extensive questioning will be recorded instead of written as not only does this speeds up the process but also considers the needs of people who have limited motor skills and other health issues such as fatigue.

I assume the answers to the four key research questions will be in written form in which case some PaMS may require additional time.

3. Involving PaMS in the planning now and in the future.

The applicant works with people with MS in his capacity as a Specialty Trainee in Rehabilitation Medicine where almost 50% of the patients have MS. The applicant has also involved people with MS via the MS Society Grant Pre-application review Research Network. I was unable to understand the information contained in the subsequent sub-heading as it contained medical terminology.

Should the study prove successful, a larger more definitive evaluation will be undertaken to investigate whether the intervention might be better tailored to meet the needs of PaMS and whether stress management can impact on disease activity. Assessing the overall cost effectiveness might also be undertaken.

Results will be published and discussed on social media.

An additional tool which I think would work very well, is a DVD of mindfulness classes supported by information presented as power points.

Reviewer #2

Question: Q1. Please score relevance and importance this project might have for people with MS.

Answer: 4 - Good

Question: Q2. If people with MS will be participants, please score how well the researchers have taken into account their needs.

Answer: 3 - Acceptable

Question: Q3a. Please score how well the researchers have involved people with MS in the planning of this study.

Answer: 1 - Poor

Question: Q3b. Please score how well the researchers have planned to involve people with MS during the study.

Answer: 2 - Needs significant revision

Question: Q4. Did you find this lay summary easy to understand and well written?

Answer: Yes

No comments.

Reviewer #3

Question: Q1. Please score relevance and importance this project might have for people with MS.

Answer: 4 - Good

Question: Q2. If people with MS will be participants, please score how well the researchers have taken into account their needs.

Answer: 3 - Acceptable

Question: Q3a. Please score how well the researchers have involved people with MS in the planning of this study.

Answer: 4 - Good

Question: Q3b. Please score how well the researchers have planned to involve people with MS during the study.

Answer: 4 - Good

Question: Q4. Did you find this lay summary easy to understand and well written?

Answer: Yes

Page16, paragraph 1: 2.5hrs seems a long time to concentrate & work. No gifts should be needed as research is for their benefit & material gain will ultimately change motivation.

Receipts should be required for transport, expenses etc

I know this seems mean but I am one of the fundraisers who collect in the wind & rain & funds are VERY hard won so should not be wasted.

Page 48 no authorised signatory?

I assume access to toilets, indoors, rails, parking, help has been suitably provided for.

Appendix B – Read Code definitions

Table B1: Read Code definitions of 31 other physical health conditions assessed.

Physical health condition	Name of variable	Definition of variable
Coronary heart disease	CHD	Read code ever recorded
Chronic kidney disease	CKD	Read code ever recorded
Asthma (active)	Asthma	Read code ever recorded AND any prescription in last year
Atrial fibrillation	Atrial Fibrillation	Read code ever recorded
Epilepsy	Epilepsy	Read code ever recorded AND epilepsy prescription in last year
New cancer in the last 5 years	Cancer	Read code first recorded in last 5 years (Relevant Read Code recorded)
Thyrotoxicosis/Thyroid disorders (includes hypothyroidism)	Thyroid Disorders	Read code ever recorded (Relevant Read Code recorded)
Diabetes	Diabetes	Read code ever recorded
Parkinson's disease	Parkinson's disease	Read code ever recorded (Relevant Read Code recorded)
Stroke or transient ischaemic attack	Stroke or TIA	Read code ever recorded (Relevant Read Code recorded)
Blindness & low vision	Blindness	Read code ever recorded (Relevant Read Code recorded)
Glaucoma	Glaucoma	Read code ever recorded (Relevant Read Code recorded)
Hearing loss	Hearing Loss	Read code ever recorded (Relevant Read Code recorded)
Hypertension	Hypertension	Read code ever recorded (Relevant Read Code recorded)
Heart failure	Heart Failure	Read code ever recorded
Peripheral vascular diseases	PVD	Read code ever recorded (Relevant Read Code recorded)
Chronic sinusitis	Sinusitis	Read code ever recorded (Relevant Read Code recorded)
Bronchitis, emphysema & other chronic obstructive pulmonary diseases	COPD	Read code ever recorded (Relevant Read Code recorded)
Bronchiectasis	Bronchiectasis	Read code ever recorded (Relevant Read Code recorded)
Crohn's disease & ulcerative colitis	Inflammatory bowel disease	Read code ever recorded (Relevant Read Code recorded)
Diverticular disease of intestine	Diverticular disease	Read code ever recorded (Relevant Read Code recorded)
Rheumatoid arthritis, other inflammatory polyarthropathies & systematic connective tissue disorders	Inflammatory arthritis	Read code ever recorded (Relevant Read Code recorded)
Hyperplasia of prostate & prostate disorders	Prostate Disease	Read code ever recorded (Relevant Read Code recorded)
Psoriasis or eczema	Psoriasis/Eczema	Read code ever recorded (M11% & M12%) AND ≥ 4 prescription in last year (BNF 13.4, excluding hydrocortisone, & BNF 13.5)
Viral Hepatitis	Viral Hepatitis	Read code ever recorded (Relevant Read Code recorded)
Irritable bowel syndrome	Irritable bowel	Read code ever recorded (Relevant Read

	syndrome	Code recorded) OR ≥ 4 antispasmodic prescription in last year (POM only, exclude kolanticon, alverine citrate & peppermint oil)
Cirrhosis/chronic liver disease/alcoholic liver disease	Chronic liver disease	Read code ever recorded (Relevant Read Code recorded)
Migraine	Migraine	≥ 4 anti-migraine prescriptions in last year (BNF 040704%, POM only exclude migraleve)
Dyspepsia	Dyspepsia	≥ 4 prescriptions in last year BNF 0103% excluding antacids AND NOT ≥4 NSAIDS OR ≥4 aspirin/clopidogrel
Constipation	Constipation	≥4 prescriptions in last year, BNF 0106%
Pain	Pain	≥4 specified analgesic prescriptions in last year (opioids/>8mg co-codamol/NSAIDS) OR ≥4 specified anti-epileptics in the absence of an epilepsy Read code in last year (gabapentin, pregabalin and carbamazepine)

Table B2: Read Code definitions of seven mental health conditions assessed.

Mental health condition	**Name of variable**	**Definition of variable**
Depression	Depression	Read code recorded in last 12 months OR ≥ 4 anti-depressant prescriptions (excluding low-dose tricyclics) in last 12 months
Anxiety & other neurotic, stress related & somatiform disorders	Anxiety	Read code recorded in the last 12 months OR ≥ 4 anxiolytic/hypnotic prescriptions in the last 12 months OR ≥4 10/25mg amitriptyline in the last 12 months and do not meet the criteria for 'Pain'
Alcohol problems	Alcohol	Read code ever recorded
Other psychoactive substance misuse	Drugs	Read code ever recorded
Dementia	Dementia	Read code ever recorded
Schizophrenia (and related non-organic psychosis) or bipolar disorder	Schizo/bipolar	Read code ever recorded/recorded in last 12 months (code dependent) OR Lithium prescribed in last 168 days
Learning disability	Learning disability	Read code ever recorded
Anorexia or bulimia	Eating disorder	Read code ever recorded

Appendix C – Sample systematic review data extraction sheet.

Data Extraction Sheet v.1Robert July 2013

Bibliographic details	
Author	Tavee
Year	2010
Country	USA
Citation	1.Tavee J, Rensel M, Planchon SP, Stone L. Effects of Meditation on Pain and Quality of Life in Multiple Sclerosis and Polyneuropathy: A Controlled Study. Neurology. 2010;74(9):A160-A.
References identified from reference list	~~yes/~~no If yes, please provide details:

Study design	Prospective non-randomised controlled trial
Study Aim	To investigate the effects of meditation on pain and QOL in MS and PN
Inclusion criteria	? any Dx of MS. (Also included a variety of PN patients)
Exclusion criteria	1) Previous meditation training in the past 6/12 2) Severe cognitive impairment 3) Unable to ambulate without assistance (EDSS >6.5)

Characteristics of study sample		
	Intervention group	Control /comparison group
Sample size	10 (19 pre drop out)	7 (11 pre drop out)
Recruited from where?	Cleveland Clinic Neurological Institute	Cleveland Clinic Neurological Institute
Gender	7F	6F
Age	48.10 (10.26)	49.29 (12.09)
Ethnicity	NA	
Socioeconomic status	NA	
Employment status	NA	
Marital status	NA	
Educational status	NA	
Living Arrangements	NA	
Other (specify)		
Multiple Sclerosis		
Definition	Medical record review by Ix team.	

Type e.g. Relapsing Remitting, 2y Progressive etc.		
Time since Dx	10.40 (6.47)	19.14 (14.15)
MS stage e.g. EDSS score	3.25 (2.2)	2.79 (2.80)
Cognitive impairment (number of participants; severity)	NA	
Affective disorders (number of participants; severity)	NA	
Co-morbidities (specify)	NA	

Mindfulness Intervention	
Definition	
Course content	Samatha (sitting and observing the breath); Moving meditation (Tai Chi, Qigong); Walking meditation. Homework encouraged.
Duration & frequency	4hr introductory session then weekly 90 minute Buddhist meditation class
Who delivered the intervention?	Buddhist monk
Did they have specific training?	NA other than taught by a 'Buddhist Monk'
No. of participants per group	19 in treatment group, 11 in control
Intervention materials	NA
Intervention location	NA
Cost to participants	NA
Cost effectiveness	NA
Transport issues	Excluded up to 16 participants overall (12 MS and 4 PN)
Family involvement	NA
Other (specify)	
Intervention for control group	
Provide details: UC and instructed to avoid meditation practices for the study duration, but offered training on completion of the study.	

Outcomes measurement		
	Intervention group	Control /comparison group
Standardised outcomes measures (specify)	SF36 QOL (mental health, physical health, vitality, physical role) MFIS - Fatigue VAS - Pain PDDS - Patient determined disease steps	

Study-specific outcomes measures (provide details)	NA	
Other outcomes measured (provide details)	NA	
No. of data collection time points	2 (baseline and intervention completion)	2 (baseline and intervention completion)
Results		
After 8 weeks, study participants in the intervention group showed a significant improvement in pain scores on the VAS (P = .035 combined group, P = .044 PN) and SF-36 scores for overall summed physical health (P = .011 MS, P = .014 PN), mental health (P = .02 combined group), vitality (P = .005 combined group), and physical role (P = .003 combined group), while no change was observed in controls. MS patients in the intervention arm also demonstrated a significant improvement in scores for bodily pain (P = .031). For the secondary outcome measure of fatigue in MS patients, improved scores were seen in the intervention group with regard to the cognitive and psychosocial components of the MFIS (P = .037, P = .032). For PN patients, a slight trend toward improvement of the motor and sensory portions of the NIS was seen (mean reduction of −0.29 and −1.5 on the NIS-M and NIS-S, respectively), but the difference did not reach statistical significance (P = .66, P = .20). No statistically significant changes were seen in PDDS scores for MS patients in the intervention group. Participants in the MS and PN control groups showed no significant improvement at the end of the trial in any of the parameters measured except for a minor improvement in mobility seen in MS patients (P = .03). Furthermore, PN controls reported worsened scores for both the VAS (mean increase in pain of 1.21 ± 2.32) and all SF-36 measures except for bodily pain and mental health. Similarly, the MS control group showed increased pain on the VAS at the end of the trial (0.50 ± 2.74) and worsened SF-36 scores for all parameters except for vitality and social functioning		
Limitations noted by the authors	Sample size small No randomisation No control group intervention Failure to record homework	
Authors' conclusions	Meditation may be helpful in reducing pain and improving quality of life in patients with MS and PN. The lack of changes seen in mobility (MS) and sensorimotor deficits (PN) suggests that meditation may not affect the overall clinical course.	
Reviewer's comments	Low quality study. Non-randomised. Intervention and who delivered it are unclear. Mixing results MS and PN make interpreting results difficult.	

Appendix D

Literature developments since completion of the systematic review

Since the systematic review was completed and published in January 2014, two further relevant studies have been published looking at the use of MBIs in people with MS. These are summarised below, along the same lines taken in the systematic review, and in order of publication, with a short section at the end listing and tabulating how these study findings compare with those of the systematic review.

1. Burschka et al. [304]

Study characteristics (see Table D1)

In Germany, Burschka et al. [304] carried out a controlled trial examining the use of a MBI. Study participants were recruited from a local hospital Neurology department, and via local MS support organisations. There were 38 participants in total; split into active (n=21) and control/treatment as usual (n=17) groups. Attrition was reported at a rate of 30% (n=6) in the intervention group (not mentioned for the control group), but an ITT analysis was not conducted - those dropping out were excluded from the analysis, which is based on data for 32 individuals. Outcome data was collected at baseline, and at the six-month point (when the intervention ceased).

Intervention characteristics (see Table D1)

The researchers employed a controlled trial, utilising a MBI which emphasised mindfulness based on the Bishop et al. [129] working definition, i.e. being composed of both self-regulation of attention, and orientation to experience (in this case primarily via breath and body awareness Tai Chi exercises). The mode of teaching was a ‘Yang-style’ Tai Chi approach, with a total of 50 (90 minute) classes being offered throughout the course of the intervention. There was no home practice, or such materials included. Also, notably, the control group had prior Tai Chi experience from earlier pilot work, and it is not clear how many of them were actually continuing to practice during the period of study.

Participant characteristics (see Table D2)

In this study, 69% (n=22) were female, with a mean (SD) age of 42.1 (8.7) years. The presence/absence of comorbid conditions, SES, level of education, and ethnicity were not delineated. The majority of participants had RRMS (85%, n=27), with four (12.5%) having SPMS, and one (2.5%) having the diagnostic label of Clinically Isolated Syndrome (CIS). Exclusion criteria were: EDSS score ≥5, current/recent (within the previous four weeks) relapse, or evidence of severe cognitive impairment. The researchers reported a higher median EDSS (4.0) for the control group, versus the median score for the intervention group (2.0).

Outcomes

The researchers were primarily concerned with measuring balance, and secondarily with fatigue, depression, and QOL. Along with co-ordination, static and dynamic balance was assessed via an established German language balance and co-ordination test [378]. Depression was assessed via the German language version of the CES-D, fatigue by the Fatigue Scale of Motor and Cognitive functions (FSMC), and QOL via the Questionnaire of Life Satisfaction. Cost/benefit was not included in the study design. No adverse events were reported.

Physical measures (see Table D3)

For balance, a significant pre-, post- improvement ($p<0.05$) in the intervention group was noted. This was associated with a significant time by group interaction. Similarly, there was a significant improvement in co-ordination ($p<0.05$) in the intervention group, which also had a significant time by group interaction. As for fatigue, there was no change in the intervention group, but a significant deterioration in the control group ($p<0.05$).

Mental health (see Table D4)

There was a significant decrease in depression scores amongst the intervention participants ($p<0.05$), whilst scores remained stable in the control group.

Psychosocial outcomes (see Table D5)

The researchers reported significantly improved QOL scores in the intervention group ($p<0.05$), which was not apparent amongst controls.

Methodological quality (see Table D6)

Going by the Cochrane Collaboration quality criteria [288], Burshka et al. [304] did not randomise, instead allocating to groups based on participant availability for the day of the intervention (High risk of bias), there was no allocation concealment (High risk of bias), they did not describe blinding of assessors, or during outcome assessment (both High risk of bias), did not follow an ITT analysis (High risk of bias), and finally, the intervention was delivered by the principle investigator (J Burschka). Overall, this means the study is at a High risk of bias, and thus low methodological quality.

2. Bogosian et al. [305]

Study characteristics (see Table D1)

In England, Bogosian et al. [305] undertook a RCT involving 40 randomised individuals, being designed to evaluate the use of a novel Skype teleconference, distant-delivered MBI. The control group received usual NHS care. Participants were recruited nationally, from across the UK, via adverts on the UK MS Society website, and from MS centres across the country. Attrition was reported as low (5%), with 18/19 of those randomised to receive the MBI completing more than four out of eight sessions; attendance was reported as 73.7% completing six or more of the eight sessions. The reasons given for the single drop out were vague (‘personal circumstances’).

Intervention characteristics (see Table D1)

The researchers piloted a live, online, ‘group’ MBI, which participants received in their own homes. Although separated in space, participants were able to see, hear, and interact with each other during the classes. The intervention was derived from MBCT,

the cognitive components having been adapted from those outlined in the original programme for depression; to focus instead on maladaptive cognitions thought to be common in the MS population. This intervention did not include any mindful movement, which the authors qualified as being guided by a small number (n=6) of case studies of people with progressive MS (Mean EDSS of 6.0), along with expert opinion from a Neurologist and MS Specialist Nurses. Again, based on preliminary work, the weekly classes (eight weeks in total) were shortened to one hour in duration, but otherwise included the recognisable core content familiar to traditional MBIs. Ten to twenty minutes of daily home practice was suggested (with accompanying CDs), but adherence rates were not reported.

Participant characteristics (see Table D2)

The study was designed specifically for people with progressive MS phenotypes, and as such excluded those with RRMS. From the total n of 40, 17 (42%) had PPMS, the remaining 23 (58%) having SPMS. Mean (SD) age of participants was 52.7 (9.5); 55% were female, mainly being British Caucasian (90%). Seventy-eight percent were cohabiting. There was no information provided regarding comorbidity or SES. The mean (SD) EDSS score was 6.5 (1.5), which is considerably higher than any of the previous studies, and median (range) disease duration was 12 (1-38 years). Exclusion criteria were a MS diagnosis other than PPMS or SPMS, not being 'distressed' at baseline (as measured by the GHQ), not having internet access, having cognitive impairment (as measured by the Telephone Interview for Cognitive Status-Modified TICS-M), hearing impairment, being deemed at high risk of suicide (measured via the Clinical Outcome of Routine Evaluation - CORE), having psychosis, or other serious mental illness. Additionally, other psychological therapies or prior mindfulness training excluded individuals from taking part.

4.7.2.5: Outcomes

The primary outcome was distress, as measured by the GHQ. Secondary outcomes included: anxiety and depression (via the HADS); mental and physical impact of MS (via the Multiple Sclerosis Impact Scale – 29 - MSIS-29); pain (via the Numerical Rating Scale); fatigue (via the Fatigue Severity Scale – FSS); QALYs (via the

EuroQol – EQ5D); and service costs (via the Client Service Receipt Inventory - CSRI).

Mental health (see Table D3)

Distress (the primary outcome measure) significantly decreased in those receiving the intervention, both at intervention completion (ES -0.67; $p<0.05$), and at three-month follow-up (ES -0.97; $p<0.05$). HADS depression improved significantly amongst those receiving the MBI at intervention completion (ES -0.65; $p<0.05$) and at three-month follow up (ES -0.53; $p<0.05$). HADS anxiety showed a similar trend at intervention completion (ES -0.40; $p<0.05$) and three-month follow up (ES -0.86; $p<0.05$). Similarly, at intervention completion MSIS-29 (psychological) had improved significantly (ES -0.99; $p<0.05$), with effects sustained at three-month follow-up (ES -1.12; $p<0.05$).

Physical health (see Table D4)

On the MSIS-29 (physical) subscale, a small significant benefit was evident at intervention completion (ES -0.36; $p<0.05$), although this narrowly lost its significance at three-month follow up (ES –0.28; $p=0.05$). For pain, no significant improvements were noted post-therapy, but were evident at three-month follow up (ES -0.59; $p<0.05$). Fatigue scores were not significantly improved at either time point.

Service use/cost effectiveness

The researchers reported that the MBI was associated (non-significantly) with reduced formal and informal service costs, and a 90% chance of being cost-effective (compared to usual care) at a threshold of £20,000. Adjusted QALYs were not different between the groups after the intervention. Societal cost-effects (generated from GHQ scores) were reported as the MBI being 87.4% more likely to be associated with cost savings.

Methodological quality (see Table D6)

Following the Cochrane Collaboration [288] guidance on risk of bias, in the Bogosian et al. [305] study there was evidence of adequate (independent, blinded) random sequence allocation (Low risk of bias); allocation was concealed from the trial assessor, the statistician and health economists (Low risk of bias); group comparisons were assessed on an ITT basis (Low risk of bias); there was no evidence of incomplete outcomes, or selective reporting of data (Low risk of bias); or any other sources of concern. This study was therefore at low risk of bias, and can be deemed a study of higher methodological quality (the only caveat being that the trial involved low numbers, and was of a pilot design).

3. Kolahkaj and Zargar [306]

Study characteristics (see Table D1)

In Iran, Kolahkaj and Zargar [306] carried out a RCT testing a MBI in people with MS. Only females with MS between the ages of 20-50 years were eligible to participate and were recruited over a six-month period from the Ahvaz MS Society via a convenience sampling technique; this meant reviewing files on record at the Ahvaz MS Society, and calling patients to invite them to participate. If agreeable to participation at this point, participants were briefed about the study, and recruited. Sixty-four people were screened for eligibility, and 15 were excluded, leaving 48 to be randomised. However, eight participants were lost to follow up, and only 40 were included in the statistical analyses; thus there was no ITT. Attrition was reported as 17%. Class attendance was not reported, nor was home practice time. Outcomes were recorded at baseline, post-intervention, and two months later.

Intervention characteristics (see Table D1)

The intervention was reported as based on both MBSR and MBCT, but was most frequently referred to in the paper as MBSR. The control group received their usual level of care. A trained psychologist delivered the intervention, but it is not clear what level of expertise in MBIs this individual held. Classes were two hours long, and took

place weekly over eight weeks. The authors reported that participants who missed classes were given additional sessions to cover the missed material and that those who missed more than two sessions were excluded from further participation.

Participant characteristics (see Table D2)

All participants in this study were female, aged 20-55, with the mean (SD) age being 25.3 (4.1), with no significant differences between the intervention and control groups. Similarly, there was no significant difference in level of education. All participants were married. Level of disability was not reported. The authors reported that any diagnosis of MS rendered a participant eligible, but later stated that having relapsing MS was an exclusion – however, this may be a mistranslation, instead possibly meaning that a current MS relapse was an exclusion criterion. Further exclusion criteria were psychotic disorder, or psychotherapy in the previous six-month period. Baseline Depression, Anxiety, and Stress Scale-21 (DASS-21) scores were higher than normative levels for depression and anxiety, but lower for stress [379].

Outcomes

Mental health (see Table D4)

The primary outcome in this study was the DASS-21. Results were reported as change in mean test scores from baseline at post-MBSR, and one month later. No effect sizes were reported. Significant improvements in all three sub-scales on the DASS-21 were reported, with a reduction in anxiety at post-MBSR that was sustained one month later ($p<0.001$); in depression at post-MBSR and one month later ($p<0.001$); and in stress post-MBSR and one month later ($p<0.001$). Improvements in depression were most notable, given that they decreased from abnormal levels (mean 8.35; SD 1.78), to well below (mean 4.80; SD 0.83) normative values (mean 6.34; SD 6.97) [379].

Methodological quality (see Table D6)

In terms of the Cochrane Collaboration quality criteria [288], the researchers in this study did randomise using a random number table, although details regarding this procedure were sparse (Unclear risk of bias). No information was provided with respect to allocation concealment (Unclear risk of bias), or whether assessor/outcome assessment blinding took place (Unclear risk of bias). There was a failure to use an ITT (High risk of bias), but no evidence of selective outcome reporting (Low risk of bias). The selection criteria, based on convenience sampling, could potentially lead to selection bias on the part of the researchers (Unclear risk of bias). Overall, this study provided vague details and thus represents an unclear risk of bias, lowering its methodological quality.

Summary of new findings (for direct comparison with systematic review findings, see Tables D1 - D6)

What do these studies add to the findings from the systematic review?

1. Bogosian et al. [305] reported statistically significant benefit in the mental health domain (anxiety, depression, distress), whilst Burschka et al. [304] also reported a beneficial effect on depression, as did Kolahkaj and Zargar [306] on depression, anxiety, and stress.

2. Burschka et al. [304] reported further significant benefit in the physical health domain.

3. Burschka et al. [304] reported significantly improved QOL.

4. Bogosian et al. [305] reported service cost savings for their MBI.

5. Bogosian et al. [305] extended the literature by including a more disabled group, finding that mental health improved in participants, even without a mindful-movement component to their MBI. They also demonstrated that shortened duration, of both classes and home practice materials may be acceptable and potentially effective.

6. Kolahkaj and Zargar [306] provided data on a previously unreported ethnic group, from Iran.

4.7.3.1: Limitations of these three studies

1. None of these studies measured mindfulness as an outcome.

2. None of these studies employed an active comparator group.

3. The vast majority of participants were female.

4. All three studies have made changes to standard MBI packages, with minimal justification.

5. Overall, study quality remains low.

Table D1 – Study characteristics

Study (Country)	**Study design** (Setting)	**Sample size** (Attrition%)	**Intervention** (duration)	**Outcome measures**	**Data collection**
Mills and Allen [289] (Wales)	RCT (Patients home)	n = 16 (12.5%)	Mindful breathing Tai Chi Self compassion Home study material (6/52 duration)	POMS Standing balance Symptom rating questionnaire	Baseline Post intervention 3 months post intervention
Grossman et al. [177] (Switzerland)	RCT (University hospital)	n = 150 (5%)	Mindful breathing Hatha Yoga Body scan Home study material (8/52 duration)	CES-D STAI MFIS HAQUAMS PQOLC	Baseline Post intervention 6 months post MBSR
Tavee et al. [290] (USA)	CT (University hospital)	n = 17 (43%)	Mindful breathing - Samatha Tai Chi (8/52 duration)	SF-36 MFIS VAS PDDS	Baseline Post intervention NR
Burschka et al. [304] (Germany)	CT (University hospital)	n = 38 (30%)	Mindful breathing Tai Chi (6/12 duration)	Balance/ co-ordination CES-D (German) FSMC QLS	Baseline Post intervention NR
Bogosian et al. [305] (England)	RCT (Patients home)	n = 40 (20%)	Mindful breathing Body scan Home study material (8/52 duration)	GHQ HADS MSIS FSS	Baseline Post intervention 3 months post MBCT
Kolahkaj and Zargar [306] (Iran)	RCT (MS society)	n = 48 (17%)	Mixture of MBSR/MBCT (8/52 duration)	DASS-21	Baseline Post intervention 2 months post MBSR

1.RCT - Randomised Controlled Trial; 2.CT - Controlled Trial; 3.CES-D Center for Epidemiological Studies Depression scale ; 4.HAQUAMS - Hamburg Quality of life questionnaire in Multiple Mclerosis (German); 5.MFIS - Modified Fatigue Impact Scale; 6.POMS - Profile of Mood States; 7.PQOLC - Profile of health related Quality of Life in Chronic disorders (German); 8.SF-36 - Short Form 36; 9.STAI - Spielberger Trait Anxiety Inventory; 10.VAS - Visual Analogue Scale for bodily pain; 11.PDDS - Patient Determined Disease Steps; 12.. FSMC – Fatigue Scale of Motor and Cognitive functions; 13 QLS – Questionnaire of Life Satisfaction; 14. GHQ – General Health Questionnaire. 15. HADS – Hospital Anxiety and Depression Scale; 16. MSIS – Multiple Sclerosis Impact Scale 17. DASS-21 – Depression, Anxiety, and Stress Scale-21; 18. NR - Not Recorded.

Table D2 – Participant characteristics

	Mills and Allen [289]	**Grossman et al**. [177]	**Tavee et al**. [290]	**Burschka et al. [304]**	**Bogosian et al. [305]**	**Kolahkaj and Zargar [306]**
Ethnicity	NR	NR	NR	NR	90% British caucasian	NR
Number of participants (% **female**)	16 (80%)	150 (80%)	17 (78%)	38 (69%)	40 (55%)	48 (100%)
Mean age (**SD**)	49.8 (6.8)	47.3 (10.3)	48.7 (11.2)	42.1 (8.7)	52.2 (9.1)	25.28 (4.08)
Socio-economic status	NR	NR	NR	NR	NR	NR
Employment status	4 employed (25%)	NR	NR	NR	NR	NR
Mean years of education (**SD**)	NR	14.1 (1.9)	NR	NR	NR, but 31 (77.5) had at least a college education	NR, but 21 had at least high school, and 19 had a bachelor's degree
Disease phenotype	SPMS 16 (100%)	RRMS 123 (82%) SPMS 27 (18%)	NR	RRMS 27 (85%) SPMS 4 (12.5%) CIS 1 (2.5%)	SPMS 23 (57.5%) PPMS 17 (42.5%)	NR
EDSS score	NR	Mean (SD) 3.0 (1.1)	Mean (SD) 3.0 (2.5)	Median (range) 3 (1 - 4.25)	Mean (SD) 6.5 (1.5)	NR
Comorbidities	NR	NR	NR	NR	NR	NR
Number taking disease modifying medication	NR	91 (60.1%)	NR	NR	NR	NR
Number taking psychotropic medication	NR	30 (20%)	NR	NR	NR	NR

1. SPMS - Secondary Progressive MS; 2. RRMS - Relapsing Remitting MS; 3. PPMS – Primary Progressive MS; 4. CIS – Clinically Isolated Syndrome; 5. EDSS - Expanded Disability Status Scale; 4. NR - Not Recorded

Table D3: Mental health outcomes

Study		**Outcome (Measure)**	**Post intervention effect size (p)**	**Follow up effect size (p) and time point**
Grossman et al. [177]	Full intervention group	Anxiety (STAI)	0.39 (0.0006)	0.36 (0.02) at six months
	Sub-group analysis		1.00 (0.002)	0.64 (0.05) at six months
	Full intervention group	Depression (CES-D)	0.65 (0.00001)	0.36 (0.03) at six months
	Sub-group analysis		1.06 (0.0002)	0.66 (0.03) at six months
Mills and Allen [289]		Anxiety (POMS)	p > 0.05*	p > 0.05*
		Depression (POMS)	p < 0.01*	NR
Burschka et al. [304]		Depression (CES-D)	p = 0.007*	NR
Bogosian et al. [305]		Distress (GHQ)	0.67 (<0.05)	0.97 (<0.05) at 3 months
		Anxiety (HADS)	0.40 (<0.05)	0.99 (<0.05) at 3 months
		Depression (HADS)	0.65 (<0.05)	0.65 (<0.05) at 3 months
		MSIS psychological	0.99 (<0.05)	1.12 (<0.05)
Kolahkaj and Zargar [306]		DASS-21 Depression	p<0.001	p<0.001
		DASS-21 Anxiety	p<0.001	p<0.001
		DASS-21 Stress	p<0.001	p<0.001

1.STAI - Spielberger Trait Anxiety Index; 2. CES-D - Centre for Epidemiological Studies Depression scale; 3.POMS - Profile of Mood States; 4.GHQ – General Health Questionnaire; 5.HADS – Hospital Anxiety and Depression Scale; 6. MSIS – Multiple Sclerosis Impact Scale; 7 DASS-21 – Depression, Anxiety, and Stress Scale-21; * Effect size not recorded.

Table D4: Physical health outcomes

Study		**Outcome (Measure)**	**Post intervention effect size (p)**	**Follow up effect size (p) and time point**
Grossman et al. [177]	Full intervention group	Fatigue (MFIS)	0.41 (0.0001)	0.38 (0.001) at six months
	Sub-group analysis		1.27 (0.0005)	1.09 (0.02) at six months
Mills and Allen [289]		Fatigue (POMS)	$p < 0.05$*	NR
		Single leg standing balance	$p < 0.05$*	$p < 0.05$* at three months
Tavee et al. [290]		Fatigue (MFIS)	$p = 0.035$*	NR
		Pain (VAS)	$p = 0.031$*	NR
		PDDS	$p < 0.05$*	NR
Burschka et al. [304]		Balance	$p = 0.031$*	NR
		Co-ordination	$p = 0.003$*	NR
		Fatigue (FSMC)	$p = 0.182$*	NR
Bogosian et al. [305]		Fatigue (FSS)	0.30 (0.15)	0.29 (0.30) at 3 months
		Pain (Numerical rating scale)	0.27 (0.20)	0.59 (<0.05) at 3 months
		MSIS physical	0.36 (<0.05)	0.28 (0.05)

1.MFIS - Modified Fatigue Impact Scale; 2.POMS - Profile of Mood States; 3.VAS - Visual Analogue Scale for pain; 4.PDDS - Patient Determined Disease Steps; 5.FSMC - Fatigue Scale of Motor and Cognitive functions; 6.FSS – Fatigue Severity Scale; 7.MSIS – Multiple Sclerosis Impact Scale; 8.NR - Not Recorded; *Effect size not recorded.

Table D5: Quality of life outcomes

Study		**Measure**	**Post intervention effect size (p)**	**Follow up effect size (p) and time point**
Grossman et al. [177]	Full intervention group	HAQUAMS	0.43 (0.0002)	0.28 (0.04) at six months
		PQOLC	0.86 (0.00000001)	0.51 (0.03) at six months
	Sub-group analysis	HAQUAMS	1.01 (0.0001)	0.58 (0.04) at six months
		PQOLC	1.71 (0.00000001)	0.51 (0.003) at six months
Burshka et al. [304]		QLS	p = 0.012*	NR

1.HAQUAMS - Hamburg Quality of life questionnaire in Multiple Sclerosis (German); 2.PQOLC - Profile of health-related Quality of Life in Chronic disorders (German); 3: Questionnaire of Life Satisfaction; *Effect size not recorded.

Table D6: Risk of bias summary

	Grossmann et al. [177]	**Mills and Allen [289]**	**Tavee et al**. [290]	**Burschka et al. [304]**	**Bogosian et al. [305]**	**Kolahkaj and Zargar [306]**
Random sequence generation (selection bias)	Low	Unclear	NA	High	Low	Unclear
Allocation concealment (selection bias)	Low	Unclear	NA	High	Low	Unclear
Blinding of assessors (performance bias)	Low	Unclear	High	High	Low	Unclear
Blinding of outcome assessment (detection bias) (patient reported outcomes)	High	High	High	High	Low	Unclear
Incomplete outcome data addressed (attrition bias)	Low	Unclear	High	High	Low	High
Selective outcome reporting (reporting bias)	Low	High	Unclear	Unclear	Low	Low
Other sources of bias (ie baseline bias)	Low	Unclear	Unclear	High	Low	Unclear

1.Low = Low risk of bias; 2.Unclear = Unclear risk of bias; 3.High = High risk of bias; 4.NA = Not available.

Appendix E – Clinician information sheet

Clinician information sheet

Study Title: Mindfulness-based stress reduction in multiple sclerosis.

Study purpose: To evaluate the feasibility, acceptability, and accessibility of a mindfulness-based stress reduction (MBSR) intervention in people with multiple sclerosis (MS).

Background: Existing evidence for psychological interventions in MS backs the use of cognitive behavioural therapy approaches (1), and some evidence also suggests that CBT derived stress modulation impacts positively on MS disease activity (2). However, beneficial results of such interventions may be short lived (2). MBSR-type approaches have good quality evidence for use in other long-term conditions (3) and are proposed to have a different mechanism of action to CBT. The evidence for the use of MBSR in MS is limited, with a small international literature leaving important gaps in the knowledge base (4).

Methods: We propose to run a randomised controlled feasibility trial for MBSR use in people with MS. It is our intention to recruit up to 50 individuals, who will then be randomised to receive either MBSR or usual care (UC). We will collect quantitative measures pre-, post- and at 3-month follow up points, using generic health related quality of life (HRQOL), the Perceived Stress Scale (5), the Multiple Sclerosis Quality of Life Inventory (MSQLI) (6), and other MBSR specific measures. We will also seek participant qualitative data on a sub-sample of up to 20 participants via semi-structured interviews. At the end of the 3-month follow up period, those initially randomised to UC will be offered the MBSR intervention.

Eligibility: Criteria for inclusion in the current study are:

1. Being >18 years of age;
2. Having at baseline a Neurologist confirmed diagnosis of MS;
3. Can understand spoken and written English;
4. Having a score of less than or equal to 7 on the Expanded Disease Disability Score (7) (Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day), in order to allow active participation in the typical Hatha Yoga Asana postures included in the standard MBSR programme.

Exclusion criteria will include:

1. Potentially life threatening physical or mental health comorbidities (i.e. suicidal ideation, active psychosis, terminal/life threatening intercurrent medical illness), or those with such conditions expected to significantly limit participation and adherence (e.g. dementia, pregnancy, ongoing substance abuse, active psychosis);
2. Those currently receiving another form of psychological intervention (non-pharmacological).

Contact details: Only those who give their permission to being referred for consideration of being included in the study, and have it recorded as such, should be referred. All potential study applicants should be referred to Dr Robert Simpson, who will carry the study phone: 07957 230 224. Dr Robert Simpson will screen all potential participants, before making a final decision on eligibility.

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Appendix F – Participant information sheet

1. **Study title**

Mindfulness-based stress reduction in multiple sclerosis

2. **Invitation paragraph**

You are being invited to take part in a research study exploring the use of Mindfulness-based stress reduction (MBSR) meditation techniques amongst people with Multiple Sclerosis (MS). Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

3. **What is the purpose of the study?**

MS is a condition that remains poorly understood and difficult to treat, from a medical perspective. It is also known that MS can be a very stressful condition to live with and thus having access to simple techniques to cope with stress seems desirable. Previous research in this area demonstrates that some forms of talking therapy that focus on changing how one thinks can help with stress in MS, but that beneficial effects tend to wear off if the contact with the therapist is lost. MBSR works in a different way from standard talking therapies and may be more or less lasting in its effects than talking therapies. It is important to answer this question in a fair way, and this trial aims to do just that by employing a randomisation process, meaning that some people will receive MBSR, whilst others wait and receive their usual care. The MBSR programme lasts for 8 weeks, and there will be a 3-month follow up period before the second MBSR group. At the completion of the study, those initially allocated to the usual care group will be offered the MBSR course.

4. **Why have I been chosen?**

This study will focus on people with MS who express an interest to take part. If you have expressed an interest in taking part, the researcher (Dr Robert Simpson) will telephone you to confirm that you are eligible to take part, and answer any questions that you may have about the study. There are certain conditions that must be met to take part, so that everyone in the trial can safely participate in the practices involved in the MBSR course.

5. **Do I have to take part?**

No, you do not have to take part in this study, and it is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason, and this will in no way affect your standard medical care.

6. **What will happen to me if I take part?**

If you agree to take part in this study, you will have the opportunity to take part in an MBSR course. A standard MBSR course focuses on teaching core ‘Mindfulness’ skills, designed to help a person deal better with stress. MBSR is delivered in a group setting, with a maximum of 25 people per group.

Mindfulness means paying attention, on purpose, to your thoughts, feelings, and experiences, in a non-judgemental, open manner. This approach has been shown to reduce stress in some groups of people living with chronic illness. The core components of MBSR are:

- Mindful breath awareness: this is usually done in a sitting position.
- Mindful body awareness: this is usually done in a lying position.
- Mindful movement: this usually involves simple Yoga postures.

The MBSR sessions last for 2.5 hours (usually with time for a tea/coffee break in the middle of this), during which time you will practise these simple exercises, as well as have the opportunity to reflect on these and feedback to the group (although such feedback is entirely optional - for example, if you do not feel comfortable about speaking in the group you will not be obliged to do so).

The facilitators of the group will be general medical practitioners (both are fully qualified GPs and Associate Specialists in Integrative Medicine), who have extensive experience in teaching Mindfulness to people with chronic illnesses and in dealing with the medical problems faced by people with MS.

It is normal practice for MBSR courses to emphasise weekly homework assignments (up to 45 minutes per day), which focus on practising the Mindfulness exercises that have been covered in the preceding class. The homework assignments are encouraged, but not essential, so that if you are unable to do them you will still be part of the group and the study. It is also asked that participants keep a diary of how often they have practised, but again, this is not essential if you find that this is too much for you to do.

All individuals completing the MBSR course will be eligible to attend a monthly 'drop-in' follow up class with the MBSR facilitators. Following all individuals completing the initial MBSR course versus usual care, and 3 month follow up, all results will be collated and analysed, before being written up as a PhD thesis.

Whether you are initially allocated to the MBSR or not, you will be asked to fill in questionnaire (which may take up to 45 minutes to complete) before the first MBSR course starts, when it finishes (eight weeks later), and then 3 months after this. These can be done from home and mailed back to the researcher (Dr Robert Simpson), who will provide stamped addressed envelopes for this purpose.

Some participants (not all) will also be asked to take part in more in-depth interviews about their experiences of the MBSR course – if you are one of these individuals you will be asked to provide separate consent for completing this type of interview.

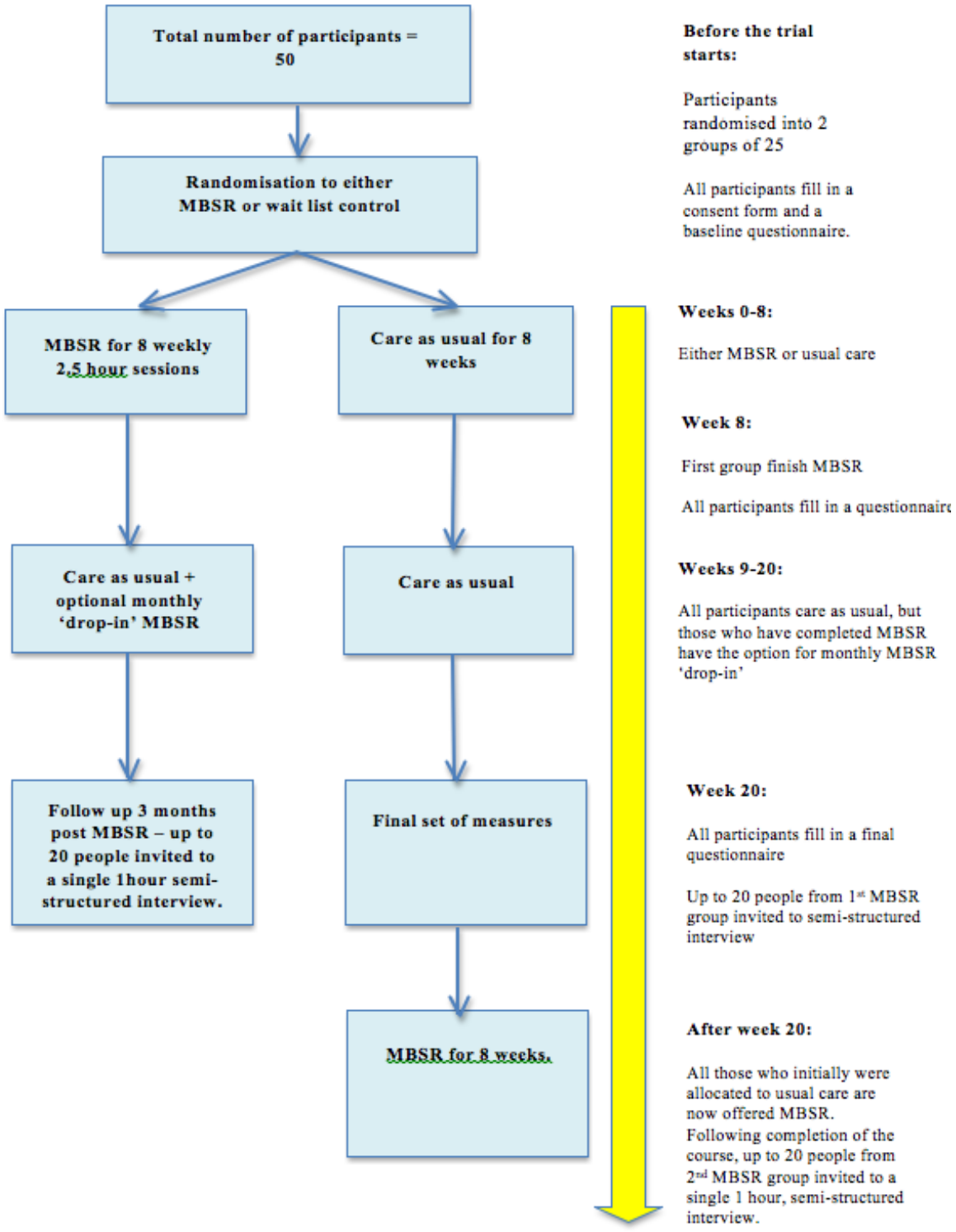
We request that you do your best to attend the MBSR course, and the sessions for filling in questionnaires, or having a more in depth interview if invited, throughout the duration of the study (however, please note that you do not have to answer any questions that you are not comfortable with, and you will not be penalised for not doing so). The researcher will be as flexible as possible with you over arranging times and dates that suit you for these purposes.

Subject to funding, you will be offered a £5 gift voucher each time you fill-in and return the questionnaire (which will be on three occasions over the course of 20 weeks, and thus £15 in total). If there are some questions in the questionnaire that you do not wish to answer (because you find them too personal or embarrassing), you will still receive the £5 gift voucher. If you are invited to take part in an additional interview to discuss your views on the intervention, you will be offered an additional £20 gift voucher. This will only happen on one occasion, towards the end of the study.

You will be involved in this project for no longer than 9 months:
- allowing us to firstly run the 8-week MBSR course once (you will either be in this group, attending a weekly 2.5 hour class for 2 months, or in the waiting list/usual care group);
- followed by a 3-month follow-up period;

- then, after that, if you were initially allocated in non-MBSR group, you will thereafter be offered the weekly 2.5-hour 8-week MBSR course at this point in time.

Please see flowchart 1 for a visual representation:



The methods used in this trial will be:

Randomised controlled trial:

Sometimes because we do not know which way of treating participants is best, we need to make comparisons. People will be put into groups and then compared. The groups are selected by a computer, which has no information about the individual - i.e. by chance. Participants in each group then have a different treatment, and these are compared. In this study, everyone will eventually be offered the chance to receive the MBSR programme. The data collected will be both of a quantitative nature (scores on questionnaires), and of a qualitative nature (semi-structured interviews, with lots of space to hear your views, unabridged).

You will be asked for your consent that your General Practitioner be informed that you are taking part in this study.

7. **What do I have to do?**

You can behave as you normally would for the duration of the trial. The only thing we ask is that if you start in the non-MBSR group, then not to start any new meditation practices out-with the trial.

8. **What are the possible disadvantages and risks of taking part?**

The only theoretical risk of taking part is that MBSR might make some people more aware of their feelings. When someone is anxious, or depressed, this might make the feelings more intense. If this happens in the MBSR class, you will be offered the chance to debrief with the course facilitators, who are highly experienced medical doctors. If this happens during an interview, you will similarly be offered a chance to debrief with the interviewer, who is a qualified General Practitioner.

9. **What are the possible benefits of taking part?**

The information that is collected during this study will give us a better understanding of stress management therapies for people with MS. Participants may also find that the MBSR helps with their own management of stress.

10. **Will my taking part in this study be kept confidential?**

All information collected about you during the course of the research will be kept strictly confidential. You will be identified by an ID number. Any information about you will have your name and address removed so that you cannot be recognised from it. Should you be invited to take part in a semi-structured interview, it will be recorded, and will thereafter be transcribed by departmental administrative staff. All transcriptions will be rendered anonymous and every effort will be made to protect your anonymity.

It is important for you to know that there are certain circumstances under which the MBSR facilitator or the researcher may have to break confidentiality. These include if someone discloses an intention to harm either themselves, or another individual, in which case the facilitator/researcher would have to inform the relevant authorities such as an individual’s own Doctor, the Mental Health Team, or the police.

Your anonymised information will be kept by the University of Glasgow for 10 years before being destroyed, in keeping with the University policies. After the researcher (Dr Robert Simpson) completes his PhD degree, your anonymised data will be kept safe by the researchers supervisors (Professor Stewart Mercer and Professor Frances Mair). You will be asked at the time of consent if you are happy to be contacted about this research following completion of the randomised controlled trial, and if you are happy that it may be used for teaching purposes. If you consent to this, you may be contacted at some point in the future (but not after 10 years time) by the researcher, or his supervisors. Should this happen, or if the data is used for teaching purposes, please be assured that your anonymity will remain protected throughout.

11. **What will happen to the results of the research study?**

All participants will be provided with a written lay summary of the findings from this study. You will not be identified in any report/publication. However, the results will be written up as part of a PhD research thesis being undertaken by Dr Robert Simpson, which will be publicly available at the time of completion (August 2015), and will also be written up in an academic journal article format, once all of the data has been analysed.

12. **Who is organising and funding the research?**

This research has been organised by researchers in the University of Glasgow, Institute of Health and Wellbeing, Department of General Practice, and has been funded by the Scottish Homeopathic Research and Education Trust.

13. **Who has reviewed the study?**

This project has been reviewed by the National Health Service Research and Ethics Service.

14. **Contact for Further Information**

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All participants will be given a copy of the information sheet and a signed consent form to keep.

15. **Thank you for reading this information sheet.**

Appendix G: MBSR course week-by-week session overview

Class (week) number	Main themes	Home practice (45 minutes daily)
1	Establishment of learning contract Theory underlying mind-body medicine and the development of self-regulatory skills Defining mindfulness Introduction to mindful eating (raisin exercise), mindful breathing, and mindful body awareness	Mindful body awareness via the body scan CD Eat one meal mindfully
2	Focused dialogue, reflection on how individual perception and conditioning affects us Affirming self-responsibility and the role of health-enhancing behaviours	Body scan CD Short sitting practices 10-15 minutes daily Reflecting on the integration of mindfulness into everyday life Pleasant events diary
3	Introducing mindful movement (flexible application of core Hatha yoga postures, mindful locomotion) Group enquiry/discussion of their experiences Review pleasant events calendar	Alternate body scan with mindful movement CD/hand-outs Sitting meditation practice 10-15 minutes daily Unpleasant events diary
4	Body scan, mindful movement, sitting meditation, with emphasis on developing concentration in the practices and an enhanced field of awareness	Alternate body scan with mindful movement CD/hand-outs Sitting meditation practice 20 minutes daily Practising awareness of stress reactions and behaviours, without taking action to change these Remaining present with 'feeling stuck/ blocking/ numbing/ shutting off'
5	Halfway point. Emphasis on development of adaptation skills, including problem-, emotion-, and solution-focussed approaches to coping, and how this relates to being aware, 'staying present', choosing more effective responses, and the development of resilience/ enhanced recovery from stressful experiences Investigating the 'shadow side' of stress responses/ trying to escape difficulty	45 minute sitting practice CD Alternate body scan/ mindful movement Complete difficult communications diary Integrate mindful awareness into daily life experiences
6	Discussion around transformation of stress coping strategies, attitudes and behaviours – developing resilience Emphasis on broadening inner resources and health-promoting attitudes and behaviours, with discussion focused on practical application Particular emphasis on stress and knowing one's feelings during communications, with overview of different communication styles	Alternate sitting meditation with body scan/ mindful movement CDs

7	Mountain meditation, introducing metaphors to reconceptualise the self as 'stable', 'flexible', and 'strong' Review of core MBSR concepts and introducing idea of choice in personal practices, but importance of maintaining 45 minutes daily Loving kindness/ compassion meditation, with strong emphasis on silence, and developing an attitude of loving kindness towards self/others	Choice between all practise introduced thus far Continued 'informal' practise in daily experiences
8	Review of core MBSR concepts. Opportunity to ask any remaining questions. Mostly silent sitting meditation Guided reflection on experience of the course Standard course evaluation forms	Optional, but strongly encouraged to continue with a daily practice of any of the core techniques learned. Integration of practices into daily life.

Appendix H - Missing data.

As the primary objective of this exploratory phase-2 study was to assess feasibility of trial procedures, no data imputation was used for missing values. This plan was agreed in advance between the researcher, his supervisors (SM, FM), and a statistician from the RCB at the University (SL). However, frequencies and percentages for all items on the respective outcome measures are recorded below (see Table H1). Rates of missing values recorded on the primary outcome measures (EQ-5D-5L, PSS-10) ranged from 0-14.4%. Rates for missing values on the MSQLI measures ranged from 0.2 – 17.2%; they were highest for the SSS, which could indicate that this is a sensitive area. The measures of mindfulness had relatively low rates of missing values at 2-22%; their being higher than the MSQLI measures could reflect the nuanced, and potentially unfamiliar language associated with the constructs. However, an anecdotal observation from the researcher (RS) was that the mindfulness measures came after the ELQ in the questionnaire packs; the wording of the ELQ was unfortunate in that if participants did not have positive responses to the questions in the ELQ, the form suggested that the questionnaire was now complete. It is possible that this led to participants thinking that they were not required to proceed on to the mindfulness measures that followed the ELQ. Further analysis confirms that this may have been the case in 6/44 (14%) individuals (P7, P8, P11, P13, P25, P27) (see Table H3). Missing values for the ELQ ranged from 0.4-14.1%.

In total, 34/50 (68%) individuals taking part returned at least one scale with some data missing. More detailed analysis of participant characteristics revealed a non-significant trend for those with missing values as more likely to be older (mean age 47.12 [SD 10.44] vs. 44.96 [SD 10.90]; p= 0.39), more disabled (mean EDSS 4.51 [SD 1.77] vs. 4.41 [SD 1.75]; p=0.40), but less deprived (mean deprivation decile 5.08 [SD 2.64] vs. 5.22 [SD 2.71]; p=0.60). The most frequently omitted question from those completing measures at each stage was Q12 from the MAAS (‘*I drive places on ‘automatic pilot’ and then wonder why I went there’*), left unanswered by four separate individuals. In future studies, should this trend recur, it might be of interest to correlate this finding with the individual’s driving status; if they were not

driving, then answering this question might not make much sense (see Table H2 and H3).

All of the measures in this study can be completed by either the individual alone, or with assistance (i.e. the researcher, or a family member/friend). In this study, the first iteration was completed with the researcher present in the room, available to assist as required. Why some measures were not completed at all in this context remains unclear (SCS-sf baseline – P27; IVIS baseline - P38; BCS baseline – P50). Besides the possibility that these participants may have felt inhibited from asking for help at the initial interview, it is perhaps easy to understand how measures might have been missed - accidentally, or through a lack of understanding when completing them on one's own. This remains an invalidated assumption from the researcher.

As a part of this analysis, the researcher sought to clarify normative values for missing values for each of the measures used. This involved literature searching on each measure, which revealed a dearth of information on the subject for all of the measures. Only the EQ-5D-5L had any information available, reporting an average level for missing values of 0.8% [380]. Rates were higher at post-MBSR and three-month follow-up. Why this was the case is not clear. For each of the other measures, the researcher contacted the respective authors via email. All reported that they had no knowledge of normative values for missing data on the measures. Thus, the researcher then spoke again with his supervisors (SM, FM), and with a senior statistician from the RCB (Dr. Alex McConnachie - AM). These discussions cemented the earlier decision not to impute for missing values, but instead to continue with the analysis in its current format, and to seek trends in the data that might help explain participant characteristics contributing to missing-ness.

In the event of proceeding to a definitive trial, missing baseline data may be included in ANCOVA models, and sensitivity analyses may be carried out, whereby the missing baseline data is imputed using multiple imputation methods. The choice of such methods would depend on the degree of missing-ness.

Table H1 – True rates for missing values for participant questionnaires.

	Participant questionnaire missing values n (%)		
Measure (total number of scale items x 50)	**Baseline**	**2-months**	**5-months**
EQ-5D-5L (900)	0 (0%)	36 (12%)	36 (12%)
PSS-10 (1500)	1 (0.2%)	72 (14.4%)	67 (13.4%)
MFIS (3150)	3 (0.3%)	109 (10.4%)	126 (12%)
MHI (2700)	3 (0.3%)	91 (10.1%)	109 (12.1%)
PDQ (3000)	4 (0.4%)	107 (10.7%)	130 (13%)
MSSS (2700)	3 (0.3%)	94 (10.4%)	110 (12.2%)
PES (900)	3 (1%)	31 (10.3%)	36 (12%)
IVIS (750)	5 (2%)	30 (12%)	30 (12%)
BCS (600)	5 (2.5%)	21 (10.5%)	24 (12%)
BWCS (750)	5 (2%)	31 (12.4%)	31 (12.4%)
SSS (750)	24 (9.5%)	43 (17.2%)	42 (16.8%)
MAAS (2250)	19 (2.5%)	94 (12.5%)	155 (20.7%)
SCS-sf (1800)	12 (2%)	60 (10%)	132 (22%)
ELQ (4950)	6 (0.4%)	171 (10.4%)	233 (14.1%)

EQ5D – EuroQol 5D-5L QOL measure; PSS – Perceived Stress Scale; MFIS – Modified Fatigue Impact Scale; MHI – Mental Health Inventory; PDQ – Perceived Deficits Questionnaire; MSSS – Modified Social Support Survey; PES – Pain Effects Scale; IVIS – Impact of Visual Impairment Scale; BCS – Bladder Control Scale; BWCS – Bowel Control Scale; MAAS – Mindful Attention Awareness Scale; SCSsf – Self-Compassion Scale – short form; ELQ – Emotional Lability Questionnaire.

Table H2 - Missing values: Any, all, or specific questions

Measure	Any missing values n (%)	All values missing n (%)	>50% missing values n (%)	Specific question numbers missing (in those completing any questions) Question number(s), Participant number(s), n/50 (%)
EQ5D baseline	0 (0%)	0 (0%)	0 (0%)	
EQ5D 2/12	6 (12%)	6 (12%)	6 (12%)	P2, P6, P21, P26, P45, P49 **all**;
EQ5D 5/12	6 (12%)	6 (12%)	6 (12%)	P2, P6, P15, P21, P26, P49 **all**;
PSS-10 baseline	1 (2%)	0 (0%)	0 (0%)	P21 **Q4** 1 (2%)
PSS-10 2/12	8 (16%)	7 (14%)	7 (14%)	P2, P6, P21, P26, P27, P45, P49 **all**; P34 **Q2** 1 (2%), **Q7** 1 (2%)
PSS-10 5/12	7 (14%)	6 (12%)	7 (14%)	P2, P6, P15, P21, P26, P49 **all**; P14 **Q2** 1 (2%), **Q4** 1 (2%), **Q5** 1 (2%), **Q7** 1 (2%), **Q8** 1 (2%), **Q9** 1 (2%), **Q10** 1 (2%) (*All from same individual*)
MFIS baseline	3 (6%)	0 (0%)	0 (0%)	P35 **Q3** 1 (2%); P49 **Q9** 1 (2%); P36 **Q19** 1 (2%)
MFIS 2/12	8 (16%)	5 (10%)	0 (0%)	P2, P6, P21, P26, P49 **all**; P29 **Q6** 1 (2%); P12 **Q9** 1 (2%), **Q10** 1 (2%); P20 **Q15** 1 (2%)
MFIS 5/12	6 (12%)	6 (12%)	0 (0%)	P2, P6, P15, P21, P26, P49 **all;**
PES baseline	2 (4%)	0 (0%)	0 (0%)	P47 **Q2** 1 (2%); P49 **Q3** 1 (2%), **Q4** 1 (2%)
PES 2/12	6 (12%)	5 (10%)	5 (10%)	P2, P6, P21, P26, P49 **all**; P41 **Q1** 1 (2%)
PES 5/12	6 (12%)	6 (12%)	6 (12%)	P2, P6, P15, P21, P26, P49 **all;**
SSS baseline	17 (34%)	15 (30%)	15 (30%)	P4, P5, P12, P13, P14, P20, P22, P27, P29, P31, P33, P37, P39, P40, P42 **all**; P17 **Q2** 1 (2%); P17, **Q3** 1 (2%), **Q4** 1 (2%), **Q5** 1 (2%)
SSS 2/12	23 (46%)	22 (44%)	22 (44%)	P2, P4, P6, P12, P13, P14, P15, P17, P19, P21, P22, P26, P27, P28, P29, P31, P33, P36, P37, P39, P40, P41, **all**; P9 **Q3** 1 (2%), **Q4** 1 (2%)

SSS 5/12	24 (48%)	24 (48%)	24 (48%)	P2, P4, P6, P9, P12, P13, P14, P15, P17, P19, P21, P22, P26, P27, P28, P29, P31, P33, P36, P37, P39, P40, P41, P49 **all;**
BCS baseline	2 (4%)	1 (2%)	1 (2%)	P50 **all**; P19 **Q4** 1 (2%)
BCS 2/12	6 (12%)	5 (10%)	5 (10%)	P2, P6, P21, P26, P49 **all;** P9 **Q3** 1 (2%)
BCS 5/12	7 (14%)	6 (12%)	6 (12%)	P2, P6, P15, P21, P26, P49 **all;** P12 **Q4** 1 (2%)
BWCS baseline	0 (0%)	0 (0%)	0 (0%)	
BWCS 2/12	7 (14%)	6 (12%)	6 (12%)	P2, P6, P9, P21, P26, P49 **all;** P29 **Q1** 1 (2%)
BWCS 5/12	8 (16%)	7 (14%)	7 (14%)	P2, P6, P15, P21, P26, P49 **all;** P32 **Q1** 1 (2%)
IVIS baseline	1 (2%)	1 (2%)	1 (2%)	P38 **all**;
IVIS 2/12	6 (12%)	6 (12%)	6 (12%)	P2, P6, P21, P26, P28, P49 **all;**
IVIS 5/12	6 (12%)	6 (12%)	6 (12%)	P2, P6, P15, P21, P26, P49 **all;**
PDQ baseline	3 (6%)	0 (0%)	0 (0%)	P36 **Q5** 2 (4%); P27 **Q7** 1 (2%); P48 **Q17** 1 (2%)
PDQ 2/12	9 (18%)	5 (10%)	5 (10%)	P2, P6, P21, P26, P49 **all;** P34 **Q1** 2 (4%); P29 **Q2** 1 (2%); P12 **Q7** 1 (2%), **Q12** 2 (4%), **Q13** 1 (2%),
PDQ 5/12	11 (22%)	6 (12%)	6 (12%)	P2, P6, P15, P21, P26, P49 **all;** P9, P19 **Q3** 2 (4%); P9 **Q4** 1 (2%), **Q6** 1 (2%), **Q8** 1 (2%), **Q11** 1 (2%), **Q13** 2 (4%), **Q16** 2 (4%) (*All from same individual*)
MHI baseline	3 (6%)	0 (0%)	0 (0%)	P20 **Q3** 1 (2%); P34 **Q9** 1 (2%); P47 **Q16** 1 (2%)
MHI 2/12	6 (12%)	5 (10%)	5 (10%)	P2, P6, P21, P26, P49 **all;** P9 **Q4** 1 (2%)
MHI 5/12	7 (14%)	6 (12%)	6 (12%)	P2, P6, P15, P21, P26, P49 **all;** Q12 1 (2%)

MSSS baseline	2 (4%)	0 (0%)	0 (0%)	P27 **Q1** 1 (2%), **Q4** 1 (2%); P29 **Q10** 1 (2%)
MSSS 2/12	8 (16%)	5 (10%)	5 (10%)	P2, P6, P21, P26, P49 **all;** P9 **Q4** 1 (2%), P20 **Q10** 1 (2%); P42 **Q12** 1 (2%); P9 **Q15** 1 (2%)
MSSS 5/12	8 (16%)	6 (12%)	6 (12%)	P2, P6, P15, P21, P26, P49 **all;** Q9 1 (2%); P20 **Q10** 1 (2%)
ELQ baseline	44 (88%)	0 (0%)	21 (42%)	P27, **Q4** (2%); P27 **Q5** (2%); P14 **Q11** (2%); P4 **Q18** (2%); P32, 39 **Q22** (4%)
ELQ 2/12	47 (94%)	4 (8%)	28 (56%)	P2, P6, P21, P26, P49 **all**; P34 **Q8** (2%); P45 **Q12** (2%); P29 **Q15** (2%); P26 **Q16** (2%); P12 **Q20** (2%); P34 **Q30** (2%)
ELQ 5/12	46 (92%)	6 (12%)	33 (66%)	P2, P6, P15, P19, P21, P26, P49 **all**; P32 **Q22** (2%); P14 **Q29** (2%)
MAAS baseline	5 (10%)	1 (2%)	1 (2%)	P27 **all**; P45 **Q10** 1 (2%); P20, P31, P33 **Q12** 3 (6%)
MAAS 2/12	10 (20%)	6 (12%)	6 (12%)	P2, P6, P11, P21, P26, P49 **all**; P17, **Q4** 1 (2%); P12 **Q10** 1 (2%); P32 **Q12** 1 (2%,); P12 **Q13** 1 (2%)
MAAS 5/12	13 (26%)	10 (20%)	10 (20%)	P2, P6, P7, P8, P13, P15, P21, P25, P26, P49 **all**; P48 **Q4** 1 (2%); P29 **Q9** 1 (2%); P17 **Q13** 1 (2%); P17 **Q14** 1 (2%), P17 **Q15** 1 (2%)
SCS-sf baseline	1 (2%)	1 (2%)	1 (2%)	P27 **all;**
SCS-sf 2/12	5 (10%)	5 (10%)	5 (10%)	P2, P6, P21, P26, P49 **all;**
SCS-sf 5/12	12 (24%)	11 (22%)	11 (22%)	P2, P6, P7, P8, P13, P15, P17, P21, P25, P26, P49 **all**; P43 **Q10** 1 (2%)

EQ5D – EuroQol 5D-5L QOL measure; PSS – Perceived stress scale; MFIS – Modified fatigue impact scale; MHI – Mental health inventory; PDQ – Perceived deficits questionnaire; MSSS – Modified social support survey; PES – Pain effects scale; IVIS – Impact of visual impairment scale; BCS – Bladder control scale; BWCS – Bowel control scale; MAAS – Mindful attention awareness scale; SCSsf – Self-compassion scale – short form; ELQ – Emotional lability questionnaire.

Table H3 – Participant characteristics for missing values

Participant number	Group allocation	Age in years	Sex M/F	Deprivation decile	Level of education	EDSS 0-7	Missing values - all	Missing values – specific questions
P2	Intervention	38	F	3	University	2.5	All measures from 2/12 onwards	
P4	Intervention	46	F	3	College	4.0	SSS baseline, SSS 2/12, SSS 5/12	ELQ baseline **Q18**
P5	Control	46	M	3	University	3.5	SSS baseline	
P6	Intervention	26	M	7	University	3.0	All measures from 2/12 onwards	
P7	Control	45	F	3	University	4.0	MAAS 5/12, SCS-sf 5/12	
P8	Control	35	M	8	University	2.5	MAAS 5/12, SCS-sf 5/12	
P9	Control	48	F	3	2y School	7.0	SSS 5/12, BWCS 2/12	SSS 2/12 **Q3**
P11	Control	42	F	1	University	4.0	MAAS 2/12	
P12	Intervention	52	F	2	University	4.0	SSS baseline	MFIS 2/12 **Q9, Q10;** BCS 5/12 **Q4;** PDQ 2/12 **Q7;** MAAS 2/12 **Q10, Q13;** ELQ 2/12 **Q20**
P13	Control	55	F	4	University	6.0	SSS baseline, SSS 2/12, SSS 5/12, MAAS 5/12, SCS-sf 5/12	
P14	Intervention	41	F	2	University	4.0	EQ5D 5/12, SSS baseline, SSS 2/12, SSS 5/12	PSS 5/12 **Q2, 4, Q5, Q7, Q8, Q9, Q10;** ELQ baseline **Q11;** ELQ 5/12 **Q29**
P15	Control	50	F	9	University	6.5	All measures from 5/12 onwards	

P17	Intervention	44	F	8	University	6.5	SSS 2/12, SSS 5/12, SCS-sf 5/12	SSS baseline **Q2, Q3;** MAAS 2/12 **Q4**; MAAS 5/12 **Q13, Q14, Q15**
P19	Intervention	63	F	9	University	7.0	SSS 2/12, SSS 5/12, ELQ 5/12	BCS baseline **Q4;** PDQ **5/12 Q3**, SSS baseline **Q1, Q3, Q4, Q5**
P20	Control	53	F	5	College	4.0	SSS baseline	MFIS 2/12 **Q15;** MHI baseline **Q3;** MSSS 2/12 **Q10;** MSSS 5/12 **Q10;** MAAS baseline **Q12**
P21	Intervention	33	F	2	College	4.0	All measures from 2/12 onwards	
P22	Control	61	F	6	University	6.5	SSS 2/12, SSS 5/12	
P25	Intervention	36	F	3	University	2.5	MAAS 5/12, SCS-sf 5/12	
P26	Intervention	40	F	4	College	4.0	All measures from 2/12 onwards	
P27	Intervention	65	F	8	2y School	5.0	PSS-10 2/12, SSS baseline, SSS 2/12, SSS 5/12, SCS-sf baseline	PDQ baseline **Q7;** MSSS baseline **Q1;** ELQ baseline **Q4, Q5**
P28	Intervention	54	F	9	University	5.5	SSS 2/12, SSS 5/12	
P29	Intervention	54	F	3	College	6.5	SSS baseline, SSS 2/12, SSS 5/12	MFIS 2/12 **Q6;** BWCS 2/12 **Q1;** PDQ 2/12 **Q2;** MSSS baseline **Q10;** MAAS 5/12 **Q9;** ELQ 2/12 **Q15, Q16**
P31	Control	51	F	3	University	1.5	SSS baseline, SSS 2/12, SSS 5/12	MAAS baseline **Q12**
P32	Intervention	27	F	6	University	6.0		ELQ baseline **Q22;** ELQ 5/12 **Q22**
P33	Intervention	52	F	1	College	6.5	SSS baseline, SSS 2/12, SSS 5/12	MAAS baseline **Q12**
P34	Control	40	F	4	2y School	4.0		PSS 2/12 **Q2;** PDQ 2/12 **Q1;** MHI

								baseline **Q9;** ELQ 2/12 **Q8, Q30**
P35	Intervention	43	F	7	University	7.0		MFIS baseline **Q3**
P36	Control	56	F	9	College	4.5	SSS 2/12, SSS 5/12	MFIS baseline **Q19;** PDQ baseline **Q5**
P37	Intervention	61	F	10	University	6.5	SSS baseline	
P38	Control	46	F	7	University	2.5	IVIS baseline	
P39	Control	21	F	6	2y School	2.0	SSS 5/12	ELQ baseline **Q22**
P40	Intervention	36	M	3	2y School	2.5	SSS baseline, SSS 2/12, SSS 5/12	
P41	Control	66	F	6	University	6.5	SSS 5/12	PES 2/12 **Q1**
P42	Intervention	40	F	4	College	1.0		MSSS 2/12 **Q12**
P43	Intervention	50	F	2	University	2.5		SCS-sf 5/12 **Q10**
P45	Control	65	F	10	College	3.5	EQ5D 2/12, PSS-10 2/12	MAAS baseline **Q10;** ELQ 2/12 **Q12**
P47	Control	38	F	6	University	6.0		PES baseline **Q2;** MHI baseline **Q16**
P48	Intervention	48	F	5	2y School	7.0		PDQ baseline **Q17;** MAAS 5/12 **Q4**
P49	Control	47	F	5	2y School	4.0	All measures from 2/12 onwards	
P50	Control	51	F	5	College	6.0	BCS baseline	
Totals	39 Intervention n=20 Control n=19	Mean 47.12 (SD 10.44)	35F (90%)	Mean 5.08 (SD 2.64)	University 22 College 10 2y School 7	Mean 4.51 (SD 1.77)	All measures from 2/12 n=5 All measures from 5/12 n=6	From partially completed scales, the most frequently missed individual question was MAAS **Q12**, at 4 individual times

EQ5D – EuroQol 5D-5L QOL measure; PSS – Perceived stress scale; MFIS – Modified fatigue impact scale; MHI – Mental health inventory; PDQ – Perceived deficits questionnaire; MSSS – Modified social support survey; PES – Pain effects scale; IVIS – Impact of visual impairment scale; BCS – Bladder control scale; BWCS – Bowel control scale; MAAS – Mindful attention awareness scale; SCSsf – Self-compassion scale – short form; ELQ – Emotional lability questionnaire.

Appendix I Unadjusted RCT patient report outcome models

Table I1: Unadjusted scores for primary outcome measures

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd'); 95% CI
Measure	Time point	Intervention	Control	Intervention	Control	N/A	N/A
EQ-5D (utility score)	Baseline	0.53 (0.23)	0.56 (0.27)	N/A	N/A	N/A	N/A
	Post	0.55 (0.23)	0.59 (0.23)	0.02 (0.18)	0.05 (0.17)	-0.04 (-0.13 – 0.06), p=0.44	-0.17 (-0.57 – 0.26)
	F/u	0.54 (0.24)	0.58 (0.28)	0.01 (0.20)	0.02 (0.17)	-0.02 (-0.13 – 0.09), p=0.67	-0.08 (-0.50 – 0.35)
EQ5D - AUC	Baseline	N/A	N/A	N/A	N/A	N/A	N/A
	Post	0.09 (0.04)	0.10 (0.04)	N/A	N/A	-0.00 (-0.03 – 0.02), p=0.82	0.00 (-0.13 – 0.09)
	F/u	0.24 (0.09)	0.24 (0.10)	N/A	N/A	-0.01 (-0.07 – 0.05), p=0.74	0.10 (-0.27 – 0.19)

F/u – Follow up; N/A – Not applicable

Table I2: Unadjusted scores for primary outcome measures

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd') (95% CI)
Perceived stress scale - overall	Baseline	21.08 (1.72)	21.96 (1.34)	N/A	N/A	N/A	N/A
	Post	13.50 (7.62)	21.77 (8.01)	-7.50 (-8.00)	-0.32 (-6.27)	-7.34 (-11.44 - -3.23), **p=<0.01**	0.93 (0.41 – 1.44)
	F/u	16.05 (7.94)	18.83 (5.93)	-4.40 (7.16)	-2.87 (4.60)	-1.51 (-5.04 – 2.20), p=0.39	0.26 (-0.37 – 0.85)
Perceived stress scale – negative stressors	Baseline	14.56 (6.09)	14.60 (4.97)	N/A	N/A	N/A	N/A
	Post	9.10 (5.26)	14.23 (5.80)	-5.00 (5.96)	-0.27 (4.76)	-4.92 (-7.86 - -1.98), **p<0.05**	0.85 (0.34 – 1.35)
	F/u	10.15 (6.55)	11.48 (5.30)	-3.75 (5.81)	-3.13 (3.60)	-0.84 (-3.60 – 1.92), p=0.54	0.14 (-0.33 – 0.62)
Perceived stress scale – stress resilience	Baseline	6.79 (2.82)	7.36 (2.72)	N/A	N/A	N/A	N/A
	Post	4.40 (2.58)	7.54 (2.91)	2.50 (2.48)	0.04 (2.64)	-2.75 (-4.21 - -1.30), **p<0.001**	0.98 (0.46 – 1.49)
	F/u	5.90 (1.92)	7.34 (1.72)	0.65 (2.28)	0.26 (2.78)	-1.31 (-2.73 - -0.25), **p<0.05**	0.51 (0.10 – 1.06)

F/u – Follow up; N/A – Not applicable

Table I3: Unadjusted scores for Multiple Sclerosis Quality of Life Inventory

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd'); 95% CI
Measure		Intervention	Control	Intervention	Control		
MFIS	Baseline	53.21 (18.68)	54.26 (16.77)	N/A	N/A	N/A	N/A
	Post	38.47 (19.84)	49.91 (17.19)	-13.33 (14.56)	-4.18 (10.87)	-9.46 (-17.24 - -1.67), **p<0.05**	0.71 (0.13 – 1.29)
	F/u	42.95 (18.58)	50.00 (15.54)	-9.5 (14.58)	-3.91 (11.15)	-5.72 (-13.10 – 1.66), p=0.13	0.44 (-1.00 - -0.13)
MHI	Baseline	68.92 (17.48)	67.45 (16.87)	N/A	N/A	N/A	N/A
	Post	83.52 (14.18)	74.22 (16.53)	13.43 (13.65)	6.10 (13.00)	8.38 (1.09 - 15.68), **p<0.01**	0.61 (0.08 – 1.15)
	F/u	78.29 (19.60)	73.41 (17.08)	8.19 (18.44)	6.25 (8.73)	2.40 (-6.46 – 11.26), p=0.59	0.17 (-0.44 – 1.09)
PDQ	Baseline	38.48 (16.24)	39.04 (14.36)	N/A	N/A	N/A	N/A
	Post	29.05 (12.31)	34.32 (14.81)	-9.00 (12.98)	-4.10 (8.77)	-5.02 (-11.27 – 1.23), p=0.11	0.46 (0.11-1.03)
	F/u	33.18 (16.94)	35.23 (14.65)	-5.47 (7.16)	-2.29 (7.71)	-2.93 (-8.00 – 2.12), p=0.25	0.38 (0.28 – 1.05)
MSSS	Baseline	44.61 (25.05)	43.12 (20.74)	N/A	N/A	N/A	N/A
	Post	45.60 (26.93)	41.45 (17.01)	-3.83 (10.62)	-0.18 (15.69)	-1.90 (-10.08 – 6.28), p=0.64	0.14 (-0.74 – 0.46)
	F/u	44.00 (25.40)	45.27 (21.36)	-6.56 (8.99)	2.45 (16.98)	-7.76 (-16.28 – 0.76), p=0.07	0.53 (-1.12 – 0.05)
PES	Baseline	17.76 (5.75)	18.17 (6.04)	N/A	N/A	N/A	N/A
	Post	14.29 (4.71)	17.00 (5.65)	-2.90 (4.13)	-1.18 (5.48)	-2.09 (-4.62 – 0.45), p=0.11	-0.43 (-0.94 – 0.09)

	F/u	14.48 (5.73)	17.22 (5.69)	-2.71 (4.82)	-1.00 (4.70)	-1.96 (-4.60 – 0.67), p=0.14	-0.41 (-0.96 – 0.14)
IVIS	Baseline	7.08 (3.29)	7.54 (3.64)	N/A	N/A	N/A	N/A
	Post	6.55 (2.52)	7.37 (3.12)	-0.85 (3.36)	-0.22 (3.16)	-0.78 (-2.32 – 0.76), p=0.31	-0.24 (-0.72 – 0.24)
	F/u	6.90 (2.77)	7.47 (3.30)	-0.38 (3.14)	-0.41 (3.23)	-0.14 (-1.67 – 1.38), p=0.85	0.04 (-0.53 – 0.44)
BCS	Baseline	9.71 (6.15)	9.33 (5.82)	N/A	N/A	N/A	N/A
	Post	7.86 (4.79)	7.61 (4.67)	-1.75 (3.94)	-1.95 (3.72)	0.13 (-1.76 – 2.02), p=0.89	0.03 (-0.47 – 0.53)
	F/u	7.90 (4.75)	8.13 (5.21)	-1.32 (4.50)	-1.09 (3.15)	-0.33 (-2.37 – 1.71), p=0.74	0.09 (-0.63 – 0.45)
BWCS	Baseline	11.87 (6.19)	9.04 (6.43)	N/A	N/A	N/A	N/A
	Post	9.80 (5.25)	8.09 (5.15)	-2.11 (2.97)	-1.09 (6.08)	0.21 (-2.41 – 2.82), p=0.87	0.04 (-0.49 – 0.57)
	F/u	10.05 (5.58)	8.09 (4.44)	-1.06 (5.24)	-1.22 (4.96)	1.27 (-1.36 – 3.90), p=0.34	0.25 (-0.27 – 0.77)
SSS	Baseline	13.00 (6.50)	13.84 (6.87)	N/A	N/A	N/A	N/A
	Post	8.80 (3.88)	14.89 (6.50)	-1.11 (4.34)	0.23 (3.56)	-2.38 (-5.53 - -0.03), p=0.13	0.62 (0.01 - 1.45)
	F/u	8.90 (4.43)	14.69 (7.00)	-1.67 (2.50)	1.64 (4.85)	-3.80 (-7.24 – - 0.01), **p<0.05**	0.88 (0.01 – 1.67)

F/u – Follow up; N/A – Not applicable

Table I4: Unadjusted scores for measures of Mindfulness and Self-Compassion

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size (Cohen's 'd'); 95% CI
Measure		Intervention	Control	Intervention	Control		
MAAS	Baseline	52.09 (17.29)	49.81 (10.89)	N/A	N/A	N/A	N/A
	Post	57.76 (9.81)	58.17 (14.06)	12.80 (10.14)	8.5 (11.60)	6.22 (-0.90 – 13.35), p=0.09	0.56 (-0.08 - 1.21)
	F/u	66.24 (7.64)	51.70 (12.60	15.6 (11.75)	1.65 (7.52)	14.67 (8.87 – 20.48), **p<0.001**	1.23 (0.80 – 1.72)
SCS-sf	Baseline	31.58 (10.17)	32.56 (8.70)	N/A	N/A	N/A	N/A
	Post	42.71 (9.80)	33.79 (10.84)	11.00 (10.21)	1.38 (8.21)	9.44 (4.21 – 14.67), **p<0.01**	0.92 (0.41 – 1.43)
	F/u	41.27 (11.75)	32.15 (9.65)	9.18 (11.05)	0.35 (7.34)	8.99 (3.09 – 14.89) **p<0.01**	0.89 (0.31 – 1.47)

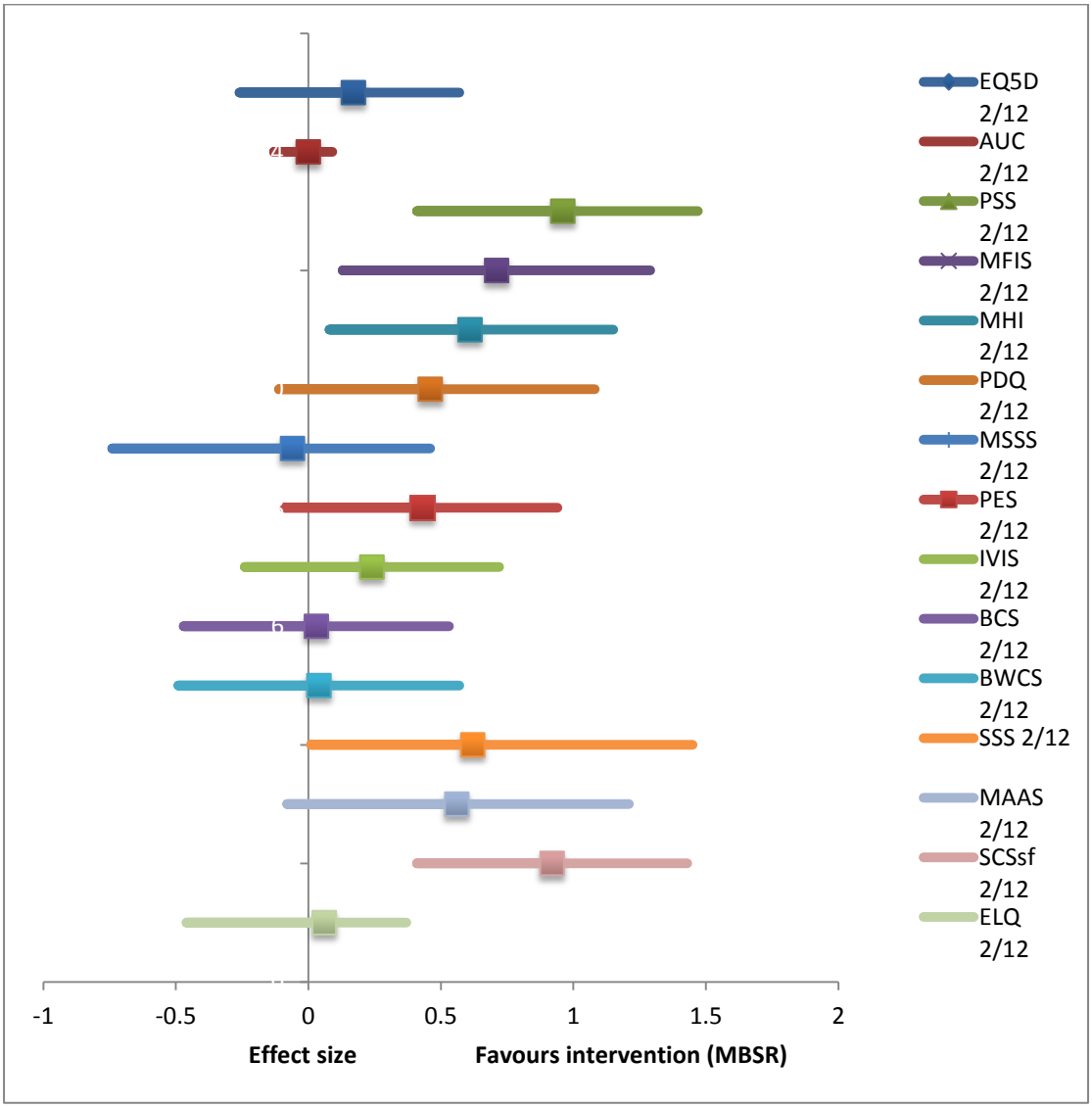
F/u – Follow up; N/A – Not applicable

Table I5: Unadjusted scores for the Emotional Lability Questionnaire

		Mean (SD)		Change from baseline		Treatment effect* (95% CI), Significance (*Intervention-control)	Effect size
Measure		Intervention	Control	Intervention	Control		
ELQ	Baseline	15.19 (14.18)	15.46 (11.33)	N/A	N/A	N/A	N/A
	Post	9.56 (10.15)	9.14 (9.56)	-5.79 (9.67)	-5.05 (8.21)	-0.55 (-5.88 – 4.76), p=0.83	0.06 (-0.46 – 0.37)
	F/u	8.72 (11.31)	11.00 (8.29)	-5.25 (13.58)	-5.12 (8.01)	-1.22 (-7.03 – 4.60), p=0.67	0.12 (-0.41 – 0.27)

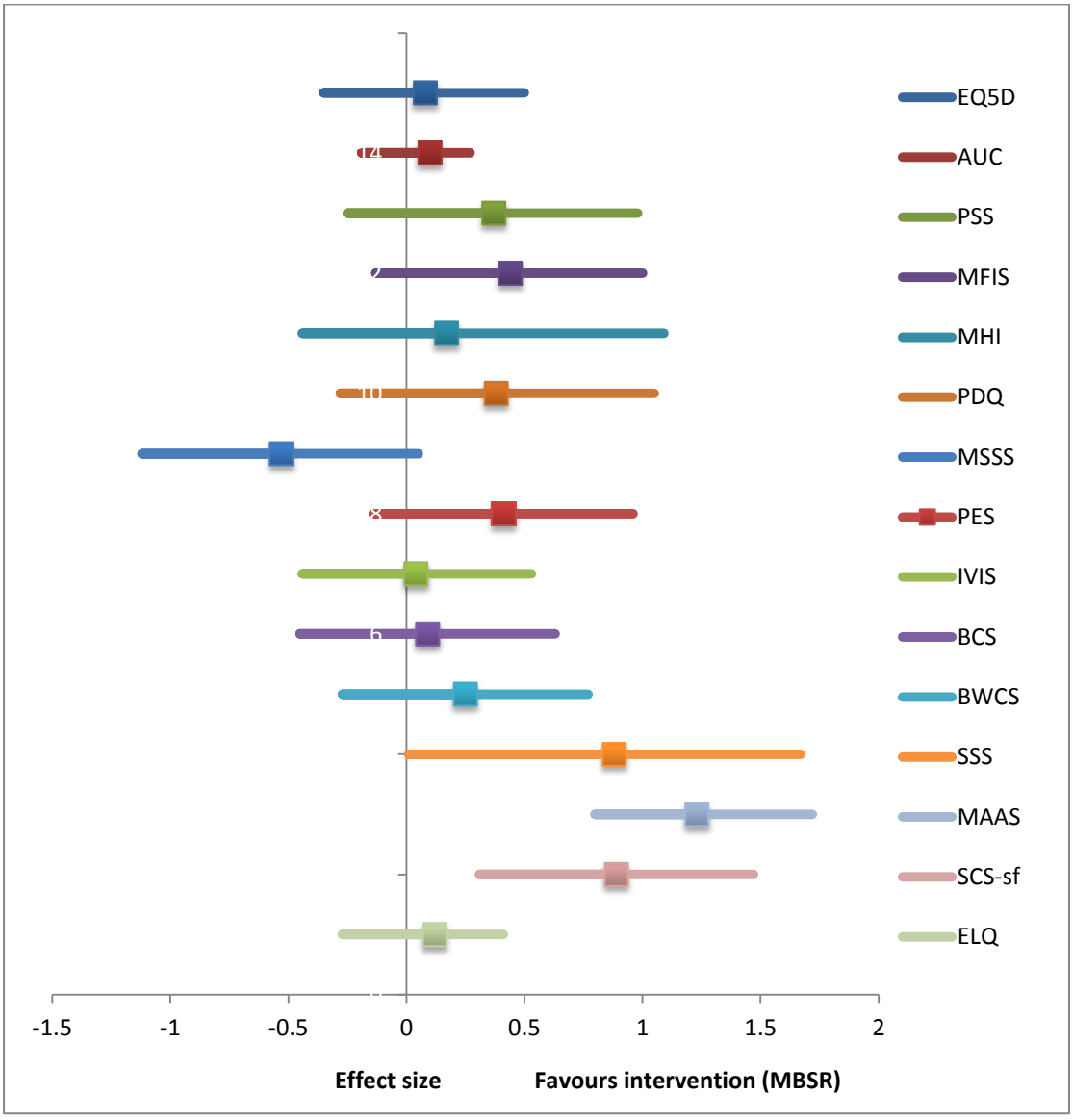
F/u – Follow up; N/A – Not applicable

Figure I1: Unadjusted treatment effects with confidence intervals for MBSR at two months**:**



EQ5D – EuroQol QOL measure; AUC – EuroQol Area Under the Curve; PSS – Perceived Stress Scale; MFIS – Modified Fatigue Impact Scale; MHI – Mental Health Inventory; PDQ – Perceived Deficits Questionnaire; MSSS – Modified Social Support Survey; PES – Pain Effects Scale; IVIS – Impact of Visual Impairment Scale; BCS – Bladder Control Scale; BWCS – Bowel Control Scale; SSS – Sexual Satisfaction Scale; MAAS – Mindful Attention Awareness Scale; SCS-sf – Self-Compassion Scale – short form; ELQ – Emotional Lability Questionnaire

Figure I2: Unadjusted treatment effects with confidence intervals for MBSR at five months**:**



EQ5D – EuroQol QOL measure; AUC – EuroQol Area Under the Curve; PSS – Perceived Stress Scale; MFIS – Modified Fatigue Impact Scale; MHI – Mental Health Inventory; PDQ – Perceived Deficits Questionnaire; MSSS – Modified Social Support Survey; PES – Pain Effects Scale; IVIS – Impact of Visual Impairment Scale; BCS – Bladder Control Scale; BWCS – Bowel Control Scale; SSS – Sexual Satisfaction Scale; MAAS – Mindful Attention Awareness Scale; SCS-sf – Self-Compassion Scale – short form; ELQ – Emotional Lability Questionnaire

Appendix J – Timeline of activities for qualitative research

31st October 2014

- MBSR intervention completed

1st Nov – 3rd Dec 2014

- Seventeen participant and two instructor semi-structured interviews carried out, mainly in office space at the NHS CIC, but also in one participant's home (as he had suffered from a relapse and had become less mobile).

4th Dec 2014 – 2nd Feb 2015

- Interview transcription by administrative staff in GPPC.

3rd Feb – 3rd March 2015

- Immersion in the audio files for the interviews. Researcher (RS) listened carefully to the content of each, and took care to cross-reference this with the typed transcripts to check their fidelity. Following on from this the researcher carried out a first sweep of the data, carefully reading through and reflecting on each interview transcript, noting down and memo-ing on interesting thoughts

4th March 2015

- Researcher randomly selected two original interview transcripts to share with his supervisors via the university shared hard-drive. The researcher's supervisors then blind coded these, ahead of the next supervision meeting.

19th March 2015

- Researcher met with his supervisors to discuss/compare notes following blind coding/first sweep of the data, focusing in particular on the two transcripts that had been sent, but also reflecting on his experience with the data corpus in general. Agreed outcome was for the researcher to move on to develop a coding index. Given the slight differences in emphasis between them, it was agreed at this point that the researcher should develop a coding index for the participants and instructors' interviews separately, with a view to possibly merging themes at a later date.

2nd April 2015

- Researcher met with supervisor (Professor Frances Mair - FM) to discuss possible frameworks for coding and thematic analysis. Researcher discussed once more the importance of reflexivity and remaining true to the original data at this point. In-vivo coding validity once more checked by supervisor (FM) from two further interviews.

6th May 2015

- Researcher met with supervisor (SM) to discuss the outline of the coding indexes he had developed, for both the participants and the instructors. For the participants, this meant a group of 45 codes, and for the instructors, 14. The researchers supervisor had applied the indexes to two further interview transcripts, noting any discrepancies, and suggesting any potential new codes that may have been overlooked, or viewed differently. Thus, any categories that were too broad were exploded, and the themes surrounding each code explored in further detail.

18th June 2015

- Researcher met with his supervisor (SM) to discuss further refinement of the coding indexes. It was agreed at this point that the researcher should now refine the initial codes (45, 14), and the supervisor provided guidance on a few examples of how to go about collapsing codes into more succinct groupings. The researcher then went off to complete this task before the next meeting, setting out on an A3 sized piece of paper a diagram detailing all 45 of the original participant, and 14 instructor codes (including examples to back these up). The researcher continued to keep this separate (on separate papers). It was agreed that over the following week the researcher would check these back with the original data, to ensure their accuracy and representativeness, in relation to the original transcripts.

23rd June 2015

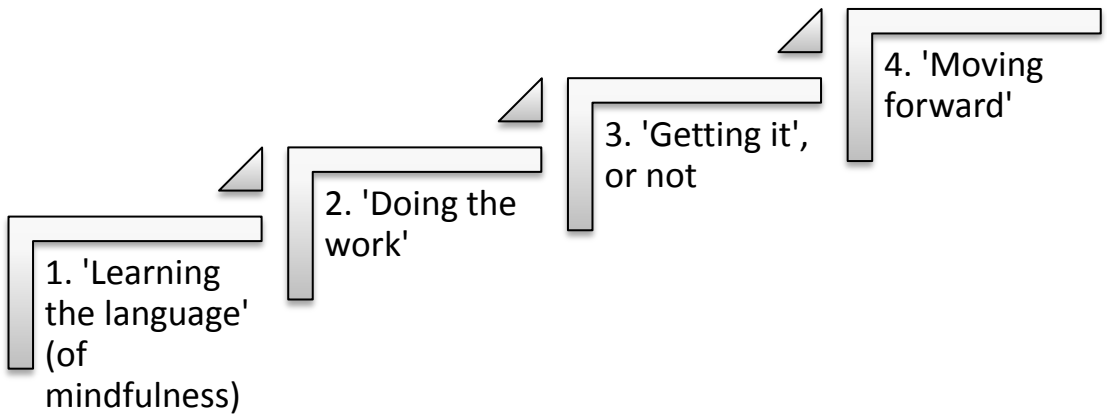
- Researcher again met with his supervisor (SM) to present an overview for each category (participants and instructors). At this session, the researcher presented the 'story' that was emerging through the refining of the codes. This session allowed reflection with the supervisor on the direction that seemed to be emerging from the data, and it was agreed that ahead of the next meeting, the researcher should aim to

finesse the coding indexes in their current form, and then attempt to ‘stand back’ from them, and take an overview of the data corpus as a whole, to include reflecting on the process of conducting the interviews, listening to the audio files, proofreading/editing the transcripts, memo-ing, and all the subsequent stages of revisiting and refinement outlined above.

2nd July 2015

- Researcher met with his supervisor (SM) to present the grouping of themes that had emerged from the data up until this point. This session again focused on a ‘standing back’ perspective, where higher order, meta-themes were discussed (i.e. those themes that were not initially obvious, but arose out of the process of iterative analysis, discussion, and synthesis of findings). Any models arising were discussed and tested against the data. One notable model that emerged was (see Figure J1):

Figure J1: An exploratory model for emergent higher order themes

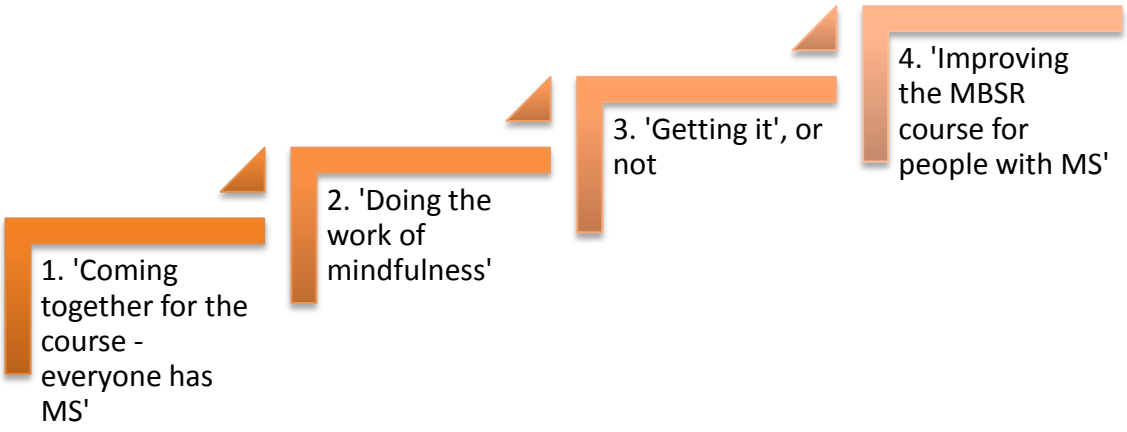


It was agreed that the researcher would test this model against the data, and refine further, as required. An important point was that it might fit one set of codes (participants), but not the other (instructors), and that whilst an attempt to merge the groups was desirable, it might not be possible. The perceived advantage was that this might allow synthesis of distinct input from participants and instructors, and the potential for emergence of further, new ‘higher order’ themes in the process.

16th July 2015

- At this point the researcher had tested and subsequently refined the above model, as it did not fit perfectly with either the individual groups, or the merged data that contained both participants and instructors' views. Indeed, the idea of learning the language of mindfulness seemed as if it might well be an implicit higher order theme in some senses, but it was difficult to group enough data with confidence under this construct. Refinement produced the following model (see Figure J2):

Figure J2: Refined model for higher order themes



This model was thus tested against the merged data, and it held up well with the original accounts. The merged categories thus formed the headings that would order and structure the results section, describing the emergent narrative from the participant and instructor experiences, in an accurate and comprehensive manner.

23rd July 2015

The researcher again met with his supervisor (SM) to discuss the synthesis of results, including how certain codes might still be amenable to being collapsed under a common heading. Thus, the thematic matrix was refined into its final form.

Appendix K - Higher order coding index – Merged themes (participant/ instructor)

1. Coming together for the course – everyone has MS

- *Pre-course expectations*
- *Being prepared and getting there*
- *Course context – getting it right*
- *Becoming a group*

2. Doing the work of mindfulness

- *Coming face to face with MS; senses, sensations, and disabilities*
- *Making sense of the practices together, in the group*
- *Making sense of the practices on one's own, away from the group*
- *Staying present or dropping out – sustaining involvement*

3. Getting it, or not

- *Being in the zone*
- *Perceived overall effects from MBSR*
- *Relating to one's self*
- *Relating to others*

4. Improving the MBSR course for people with MS

- *Being better prepared*
- *Making MBSR more relevant to people with MS*
- *Improving delivery strategies of MBSR for people with MS*
- *Timing; when is the best time to learn MBSR if you have MS?*

Appendix L – Thematic matrices 1-4

1. Coming together for the course – everyone has MS	**1.1**	**1.2**	**1.3**	**1.4**
Subject no **No. sessions attended** **Age** **Sex** **Ethnicity** **Deprivation decile** **Education** **EDSS** **MS phenotype** **MM count (MH)** **MHI baseline score**	**Pre-course expectations**	**Being prepared and getting there**	**Course context – getting it right**	**Becoming a group**
No. 1 Att: 7/8 52F White Scottish DD 2 University EDSS 4 PPMS	Unsure, willing to try anything that was going to help, thought it might help with stressful situations	Was off work with wrist fracture so had time available (otherwise it wouldn't have worked for pt), parking was an issue, took the train	Setting was fine, preferred the upstairs room as it was more intimate, second room was bigger, colder and had more distractions Thought week 1 was not well set up for those with disabilities Thought room 6 temperature was not ideal and lighting too bright	Found working as a group beneficial, everyone in same boat (a 'unity'), instructors good and engaging Pt thought that the instructors were good and engaging

3 (1) **69**				
No. 2 Att: 6/8 41F White Scottish DD 2 University EDSS 4 RRMS 3 (1) **46**	Unsure, a bit reserved, worried about speaking in the group	Pt lived quite far away. Found parking ok. Centre hard to find with no street names. Wasn't able to come when had an illness. Morning not a good time for pt.	Pt would have preferred a morning class, more together then, normally naps in afternoon. Found setting lovely, less clinical, 'a pleasant surprise', preferred downstairs room and view out to the garden Wished course could have lasted for longer. 2.5 hrs seemed a lot at the start.	First thing on arrival was to do a meditation, which calmed and relaxed pt right away, calmed nerves and anxiety Pt liked hearing others experiences as they were similar to her own, and this validated her own in a way. Normally never meets others with MS Instructors put pt mind at rest 'you don't have to talk if you don't want to'. Pt then found she wanted to and was so relaxed after meditating that this was easier than expected
No. 3 Att: 8/8 54F White Scottish DD 9 University EDSS 5.5 PPMS 0 (0) **64**	Didn't have any expectations, was open minded and thought it was worth trying Was not expecting HP	Pt drives and parking was ok for pt Pt noting that for those who couldn't drive, getting to the Centre could have been difficult, getting on and off buses etc As course fell over lunch hour, pt had to adjust her eating routine	Pt noting that everyone appreciated and spoke about the garden, with the beautiful autumn colours. Found it peaceful, with a lovely atmosphere. Ground floor (room 6) had good disabled access Pt noting course fell over lunch hour and people with MS can easily get fatigued Thinks 8/52 required to embed the practices fully 2.5 hours ok with a break	Liked the group format, and got a lot out of it, liked speaking to others about their perspective and feedback. Found it interesting to see how people were reacting to things. Thinks it doesn't happen naturally to find yourself in a group of people with MS. Pt describing how the old cliché 'what happens in the room stays in the room' helped people trust and open up about personal issues, knowing they wouldn't find their details turning up on the social media etc. Felt this gave the group a real positive feeling Pt notes that if people didn't want to speak in the group, that 1 to 1 was available at the end of the sessions
No. 4 36M Att: 7/8 White Scottish	Pt thought that people with MS would find 'sitting' difficult	Pt initially drove, but found parking difficult, eventually giving up and taking the bus instead. This meant much longer journey times in both	Pt found strip lighting gave him a headache and reclined seats in room 6 made it difficult not to get sleepy Thinks course should have been	Pt found it insightful to see others with MS at different stages and to compare to his own experiences with the condition Pt liked being in a group as he is a

DD 3 2y school EDSS 2.5 RRMS 9 (3) **58**		directions	longer	'loner' and this made him deal with his social anxiety. Felt sad seeing others suffering. Had never been in a group of people with MS before
No. 5 Att: 7/8 65F White Scottish DD8 2y school EDSS 5 RRMS 9 (2) 75	No expectations, but willing to try new things unless good reason not to do so		Pt liked the view out to the garden from room 6. Thinks 8/52 good as each week had a lot of material to cover. 2.5 hrs ok, and passed quickly	Enjoyed the opportunity to meet others with MS, which she would otherwise rarely do Felt more understanding of others problems and how similar they were to her own
No. 6 Att: 7/8 44 F White Scottish DD 8 University EDSS 6.5 RRMS 5 (2) **49**	Pt was keen to reduce stress, wanted to feel more balanced in her attitude towards life, hoped would derive some physical benefits	Pt found parking traumatic and stressful. Had to leave the house an hour before class started	Pt was annoyed by hospital policy regarding taking drinks into the seminar room in case of damaging the carpets. Waiting room was difficult for pt to navigate due to crutches and would have preferred direct access to the room to settle herself Pt found there was a 'wall of heat' that met her in room 6 Pt felt her blood sugars were 'all over the place' Pt thinks 8/52 good, but was a lot for her	Pt found it difficult seeing others in week 1 who were more disabled than her Pt found instructors patronizing and that when pt raised a concern about MW one off them put her down. Also pt had to leave for the toilet and was apparently told to stay until the end, which she found embarrassing. Noting that with MS you might not have much time to make it to the toilet
No. 7 Att: 3/8 52F White Scottish	Had thought there would be more meditation practices, but that class times would be shorter	Pt lived nearby, which helped. Pt found parking an issue, on one occasion having to park illegally – was issued a ticket, but had it rescinded.	Pt thought the lift was small and notes that on week 1 the upstairs disabled toilet wasn't working, meaning people had to go	Pt thought being in a group was an advantage in some ways, valuing the opportunity to share experiences, but does notes that people with MS can tend

DD 2 College EDSS 6.5 RRMS 5 (1) **63**		Takes pt a few hours to get going. Was late on one occasion and decided not to come	downstairs/take the lift Pt noted a distracting ticking clock in room 6 was removed the following week Pt felt 12 noon was early enough, and that people need to make arrangements to get here etc, and that Friday is a busy traffic day. Thinks 8/52 too long, and content could be covered in less time. 2.5 hrs ok	to focus on the negatives Pt described the instructors as lovely, and encouraging
No. 8 Att: 7/8 34F White Scottish DD 3 University EDSS 3.5 RRMS 5 (1) **72**	Pt was a bit wary, not knowing much about Mindfulness. Tried to be open minded Wanted to reduce stress, pain Pts expectations were exceeded as she never thought simple exercises like those on the course could alleviate pain		Pt thought the Centre was wonderful 'a box on nature'. Liked looking out to the garden. Pt appreciated room 6 lighting could be adjusted. Pt likes it because its not like a hospital (grey/bleak/smell of cleaning fluids), where Drs (especially Neurologists) act aloof. Pt thought afternoon timing was soothing, and that she is not a morning person Thinks 8/52 ok, but could have gone on for longer	Pt found it really good to meet other people with MS, as she only knows one other person with the condition. Pt thought it was an advantage that everyone had MS as they were 'all in the same boat' together Pt thought that as everyone had MS, you didn't have to explain, people just understood, e.g. if you were tired they wouldn't ask did you need more sleep, or coffee Pt thought the instructors were flexible and that they could move about if they needed to
No. 9 Att: 2/8 48F White Scottish DD 5 2y school EDSS 7 RRMS 1 (0) 84	Pt thought course would be more focused on MS and ways she could make herself better, that there might be exercise included in it, or other ways to push yourself to do better Wondered if she might be able to say something to help others in the group		Thought the venue was fine, as was time of day, course duration etc. 2.5 hrs felt like 9hrs for pt	Pt liked that others were expressing their problems and this made her feel less alone Pt thought the instructors were really nice

No. 10 Att: 7/8 43F White Scottish DD 7 University EDSS 7 RRMS 1 (0) **71**	Pt was skeptical, having not done anything like it in the past. Thought getting anything out of the course would be a bonus	Pt was reliant on others for transport and getting there, with a 1 hour journey each direction. Finds sitting in a car difficult, meaning that she was tired by the end of the day.	Thought the venue was really nice Room 6 was very noisy, but liked the view out to the garden Room 6 was too hot Pt noting time of day might be an issue for those depending on transport Thought 8/52 fine. 2.5 hrs fine	Pt thought that as everyone was in the same position they made allowances for each other Pt found the instructors easy to listen to and soothing, and couldn't do enough to help
No. 11 Att: 8/8 27F White Scottish DD 6 University EDSS 6 RRMS 4 (1) **66**	Didn't know what to expect Hoped to come out on the other side better		Awkward time of day for pt, an 'eating time', had to eat an early lunch, as did her toddler, missed a medication dosage. Thought might be nice for course to go on for longer 2.5 hrs initially felt like a lot but later flew by	Pt felt the same as the other pts, and that 'everybody understands'
No. 12 Att: 5/8 38F White Scottish DD 3 College EDSS 2.5 RRMS 5 (2) 79	Pt had previously done an introductory Mindfulness course, which helped with stress and some physical symptoms like a lump in her throat.		Pt thinks that firstly the seminar room wasn't big enough on day 1, and then afterwards room 6 wasn't big enough for the Mindfulness practices (MW/MM) Time of day fine Liked 8/52 duration	Pt liked hearing others views, which on occasion surprised her Pt liked being in group with other people with MS as they were all there for the same reasons and understood each other Pt found the instructors organized and disciplined
No. 13 Att: 1/8 46F White Scottish DD 3	Pt hoped for new techniques/tools for helping to deal with stress/pain/sleeping difficulties	Pt found parking difficult.	Pt was quite upset that better provisions had not been made for people with wheelchairs, for example, no spaces in the semi-circle of chairs – this is a bug bearer of hers	Pt found seeing people more disabled than her hurt her as she felt she was sseing the range unfold in front of her Pt liked the social aspect of the session she attended, and that others were open

University EDSS 4 RRMS 8 (0) 100			Pt thinks Centre is lovely, with nice views Time of day/2.5hrs fine	and supportive, giving her empathy for her tears Pt felt able to hide her annoyances in the big group Pt felt there was an assumption on day 1 that everyone knew what Mindfulness was all about and there was some jargon being used Pt describes the thumbs up/down safety mechanism if someone became distressed Pt found one of the instructors like a headmistress
No. 14 32F Att: 8/8 White Scottish DD 10 College EDSS 4 RRMS 6 (2) **42**	Pt thought she had nothing to lose and was willing to try anything that might help			Pt made a couple of friends for life and started an email group so that everyone could stay in contact. Noting that pts 'could vent to each other' Pt thinks the response from the instructors to the difficulties of week 1 was good and changed the whole attitude of the group
No. 15 Att: 1/8 40F White Scottish DD 4 College EDSS 1 RRMS 2 (0) 103	Was keen to be in a clinical trial that might lead to new Rx for people with MS Expected course to be more interactive and for there to be more meditation		Pt thought the Centre was alright, with plenty of space Time of day ok Pt thinks that 2.5 hrs is too long, especially for people expected to sit for that time	Pt commenting on seeing others more disabled in week 1 and how this emphasized the ruthless nature of MS Pt does not know anyone else with MS Pt thought it was good to see/hear how others were experiencing MS, but that being in the group was 'total conflict' and that people were moaning and thinking themselves unwell. Pt felt this was a 'greetin meeting' and a risk to her health. Ins called pt after she dropped out and pt

				found her challenging on the phone
No. 16 Att: 7/8 44M White Scottish DD 8 University EDSS 6.5 RRMS 0 (0) **53**	Pt was cynical about 'all that sort of stuff' but had Googled Mindfulness and was surprised by how mainstream it was, with BBC coverage and pt testimonials		Pt liked the setting for the Centre, and that it was modern, and less clinical than the other hospitals he attends which are filled with sick people. Was disgruntled that the course was making people with MS walk up stairs, and was tired by the time he had walked along the corridor to the seminar room Pt liked settling himself in the waiting room before the class Room 6 was too noisy. Pt would prefer 230pm start, around time of finishing work 2.5 hrs flew by	Pt thought the RE was weird Thinks it was an advantage that everyone had MS, but notes that it was 'hard not to start a bitching session', which could make staying on track difficult Preferred group format to working in pairs as it is less 'up close and personal'
No. 17 Att: 6/8 36F White Scottish DD 3 University EDSS 2.5 RRMS 2 (1) 75	Expected to benefit		Pt comments on Ins apologizing for the difficulties of week 1 and making improvements, which were appreciated Friday was good for pt, more relaxed. As was time of day. Felt 8/52 about right. 2.5hrs flew by	Pt thought that the instructors were very good at listening and showing empathy, as well as directing the flow of the conversation
Course instructors				
I1	Ins thought it would be the same as any other course			Ins describing the paired off get to know one and other introductory exercise they normally use backfiring so that what everyone reported as having in common was simply MS

				Ins thinks there was a a lot of comparison going on between pts
I2	Ins thought that because there had been screening and recruitment that it might be an easy course, with high levels of motivation from those taking part	Ins noting that she thinks parking is a real problem at the Centre, and that the buses do not drop off at this particular building. Also noting that hospital transport is unreliable, and hence not allowed for the course, as it leads to interruptions with people coming and going at unhelpful times.	Ins commented on the rule about not bringing drinks into the seminar room and how this was difficult for people with a dry mouth, or needing to take medication etc Ins spoke about the MDT in the Centre pulling together to deal with the difficulties that had arisen in week 1. Specifically the PT moving the class, the nurses helping with pts, and the tea/coffee being brought to the room.	

2. Doing the work of mindfulness	**2.1**	**2.2**	**2.3**	**2.4**
Subject no No. sessions attended Age Sex Ethnicity Deprivation decile Education EDSS MS	**Coming face-to-face with MS: senses, sensations, and disabilities**	**Making sense of the practices together, in the group**	**Making sense of the practices on one's own, away from the group**	**Staying present, or dropping out – sustaining involvement**

phenotype **MM count (MH)** **MHI baseline score**				
No. 1 Att: 7/8 52F White Scottish DD 2 University EDSS 4 PPMS 3 (1) **69**	Pt feels more accepting towards her MS and the way she thinks about her sensations, and this has made her feel more relaxed about having MS and what each new Sx might mean		Pt commenting that being asked to do HP was like being at school, which she rebelled against, but did do the HP because she felt she wanted to Pt noting that other things going on in the house acted as a distraction	Pt found that the group inspired her to attend the course, felt that she had to attend regularly and not miss sessions in order to derive the benefit Pt missed the MW and had to try and learn it from the book
No. 2 Att: 6/8 41F White Scottish DD 2 University EDSS 4 RRMS 3 (1) **46**	Pt feels happier and more excited about speaking to Drs about her MS	Pt prefers MBSR to taking medication, which she describes as artificial and limited in duration of effect	Pt commenting that initially thought shorter HP would be easier, but that in fact the reverse was true. Found it harder to remember to do the shorter practices and that it was easier to get into it in a longer practice. Had to make it clear to kids that this was her time	Missed one session through illness Pt missed the MW day and is not sure how to learn it
No. 3 Att: 8/8 54F White Scottish DD 9 University EDSS 5.5 PPMS 0 (0)	Pt feels more accepting towards her MS Feels like she can use her mind to heal her body		Pt noting that as she was living in her fathers house, she had to create a space to practice in, somewhere peaceful where she could concentrate	

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No. 4 36M Att: 7/8 White Scottish DD 3 2y school EDSS 2.5 RRMS 9 (3) **58**		Pt thought the MBSR practices were 'like learning to walk again in Mindfulness terms' Pt makes reference to his own understanding of the practices and their relationship with 'Prana' Pt found discussing experiences with others tedious		
No. 5 Att: 7/8 65F White Scottish DD8 2y school EDSS 5 RRMS 9 (2) 75		Pt found MW in the group difficult as she has vertigo, but was fine in the house, where she can hold on to things and falling doesn't matter as much	Pt noted that even though she has time available in the day, it was difficult to allocate time for the HP. Pt states that it was easier to practise if her husband was out golfing, as if he were at home she would just watch TV with him. Preferred MBCT book to FCL.	Pt stating that she committed to the 8 weeks and that if she commits to something she likes to see it through Missed one session through illness and not wanting to spread it to others
No. 6 Att: 7/8 44 F White Scottish DD 8 University EDSS 6.5 RRMS 5 (2) **49**	Pt felt that a lot of emphasis was put on the senses in week 1, and notes that this can be challenging for people with MS. Pt found MM difficult as she couldn't do hand exercises and this accentuated her sense of disability However, pt feels the Mindfulness takes the focus off the illness/ pain/ disability	Pt thinks MBSR course has provided her with food for thought in relation to thoughts and emotions Pt found MW very difficult, accentuating her sense of disability Pt found enquiry process very intense and this put her off contributing as she didn't feel she had the energy for it		

No. 7 Att: 3/8 52F White Scottish DD 2 College EDSS 6.5 RRMS 5 (1) **63**		Pt thinks enquiry process laboured the point too much and that pts didn't know how to answer and eventually just said whatever they felt the ins wanted them to say		Had a flare of arthritis which meant missing one session
No. 8 Att: 7/8 34F White Scottish DD 3 University EDSS 3.5 RRMS 5 (1) **72**		Pt didn't initially like MW in the group as it made her feel like being back at school in a line up, felt vulnerable. Found looking at feet and walking difficult. Really got into the MW at home and enjoyed exploring nuances of it Pt was surprised to learn that others were experiencing the practices differently to how she was	Pt noting that being told to do the HP by a Dr makes her more likely to do it Pt noting that noises in the house were distracting	Missed one session through illness Pt commenting that seeing that the Drs were into the practices acted as an inspiration, helped the pt look forward to learning new things and to carry on
No. 9 Att: 2/8 48F White Scottish DD 5 2y school EDSS 7 RRMS 1 (0) 84				Pt dropped out as she felt course emphasis and participants were too negative. Pt prefers a positive attitude, pushing herself, and more exercise. Thinks she is not a 'relaxation person'
No. 10 Att: 7/8 43F White Scottish DD 7				Pt likes to see through things she has committed to. Had to force herself on a few occasions where she was tired, or not feeling well

University EDSS 7 RRMS 1 (0) **71**				
No. 11 Att: 8/8 27F White Scottish DD 6 University EDSS 6 RRMS 4 (1) **66**	Pt did not like the RE as it made her more aware of her visual impairment	Pt thinks no one liked MW in the group and that everyone 'freaked'. Pt felt ridiculous 'staggering about the room'. Pt kept practising it as HW	Pt relays a story where she told ins in class that she hadn't done the HP. Ins asked her why are you here? and this made pt reflect and realize that in order to give herself a chance at benefit, she would have to do it. This made her determined	Pt was determined to get to the course and in order to do this, had to organize things better
No. 12 Att: 5/8 38F White Scottish DD 3 College EDSS 2.5 RRMS 5 (2) 79	Pt thinks from practising Mindfulness, her MS Sx have become less apparent	Pt had taken previous intro course to Mindfulness. Found MBSR self compassion practices difficult, prompting a deep inner enquiry and history of abuse Pt found MW unsettling, brought into awareness aspects of her walking that were not good. Pt still practising, finds this challenging, but likes the challenge		Pt had a relapse during course (switching from one MS drug to another). Found relapse a lot less difficult than previously and puts this down to practising mindfulness during it.
No. 13 Att: 1/8 46F White Scottish DD 3 University EDSS 4 RRMS 8 (0) 100	Pt felt RE was focusing in on where she is worst affected. Felt obliged to continue for sake of group. Sx came into sharp and painful focus, and hammered home sense of disability			

No. 14 32F Att: 8/8 White Scottish DD 10 College EDSS 4 RRMS 6 (2) **42**			Initially, pt just wanted HP to be over and done with, but by about week 3-5 something changed and she was then looking forward to the HP as it was relaxing and good for her	Pts Mother and MS Nurse encouraged her to attend, both of whom she respects Seeing other pts drop out inspired pt to keep going
No. 15 Att: 1/8 40F White Scottish DD 4 College EDSS 1 RRMS 2 (0) 103	Pt recounts how another pt got upset in RE as it focused her attention on something she couldn't do. Pt thought this represented a misdirection for the course to focus on disability	Pt notes that in Sahaja meditation there is no focus on any particular condition, whereas the Mindfulness course focused too much on the physical, which she thinks is not good for MS pts		Pt commenting on another pt (26/6 yo M) who dropped out after week 1. Thinks he was disillusioned with respect to his future with having MS. Pt felt course focused too much on disability. Felt group need counseling, not meditation, and that they were having a 'greetin meeting', grieving for the lives they had lost to MS
No. 16 Att: 7/8 44M White Scottish DD 8 University EDSS 6.5 RRMS 0 (0) **53**	Initially pt did not get the purpose of the RE, but does now, having completed the course Pt found that being asked to write was embarrassing because his tremor makes this barely legible			Pt felt obliged to attend as the course had been set up and run by 'you guys' Pt had a UTI and relapse at week 3. This made pt 'take the huff with life' and stopped doing HP from this point, thinking 'what's the point?' Did continue to attend classes though, only missing one, where he couldn't walk
No. 17 Att: 6/8 36F White Scottish			Pt noting that she might find it easier to implement the HP if she weren't back working. Found it difficult to prioritise time for it, and instead did the housework	

DD 3 University EDSS 2.5 RRMS 2 (1) 75				
Course instructors				
I1	Normally starts with RE, thinks it's a lovely sensory exercise for people Never seen someone cry in it Recognised a need to become vigilant Thinks pt was hypersensitive and then 'numbed out' to deal with this, and noting this might be a theme with MS as a condition Ins thinks MS a very difficult condition with serious consequences. Ins felt Mindfulness would be very beneficial for people with MS, in particular to feel more in charge of themselves Ins makes note of MS pts being hypersensitive, or numb, both physically and emotionally. Ins talks about benefits of paying attention, noticing, checking thought content etc and bringing compassion to a struggling body	Ins noting MW was very difficult, a lot of pts didn't like it, and the group required a lot of holding by both ins' which was hard Ins describes how other ins brought in some writing about another WC pt's experience of MW and how he adapted to it and found benefit	Ins notes that they let people know at start of course that HP will be there and that those who do it are likely to benefit most. Ins notes that weeks 1-3 are important HP times, as this is where a 'bedding in' of the practices takes place. Ins felt that HP was not being done so put in an intervention by reading an excerpt from FCL to the group emphasizing that its hard, but you just need to do it	

I2	Realised things not going well, started to panic, wanted pts to feel comfortable Ins thought pts were sticky with respects to their MS Dx, and referred to previous experience with CFS pts. Thought pts were looking for special dispensations Ins mentions the idea of how in MS the body has turned against itself – thought this was an interesting area to examine the role for compassion towards the body		Ins thinks HP very important and that the evidence says that those who do it benefit most. Notes that they have changed name from HW to HP, as people don't like feeling that they are being told what to do	Ins thinks that the set up had not been right for people with disabilities/ needs of people with MS on day 1. Ins makes note of the importance of the OS, giving people a chance to know what they are in for with the course, and a chance to leave gracefully Ins routinely phones drop outs and feedback she got was that people who had had wanted more focus on the positives, and seeing others more disabled with MS was difficult for people

3. Getting it, or not	**3.1**	**3.2**	**3.3**	**3.4**
Subject no No. sessions attended Age Sex Ethnicity Deprivation decile Education EDSS MS phenotype	**Being 'in the zone'**	**Relating to one's self**	**Relating to others**	**Perceived overall effects from MBSR**

MM count (MH) MHI baseline score				
No. 1 Att: 7/8 52F White Scottish DD 2 University EDSS 4 PPMS 3 (1) **69**	Pt found sitting practices uncomfortable, so tended to avoid these, opting for lying instead During the BS, pt was able to change how she related to sensations in her body	Pt describes recognizing the signs that her mood is dropping, and being able to intervene then	Pt more aware of others perspective, especially that of her children	Pt feels calmer, less stressed and less uptight
No. 2 Att: 6/8 41F White Scottish DD 2 University EDSS 4 RRMS 3 (1) **46**	Initially pt struggled to see the point of the practices, but during the Mountain med something clicked for pt, felt fantastic and this feeling lasted, making doing the practices easier Pt found starting the group with a meditation helped her to relax and get into the mood for it	Sees Mindfulness practice as her time, not to be interrupted by kids	Pt feels more connected with her children and they have commented that her MS had 'stopped working' Pt is using her mindfulness skills with her son, who she thinks is naturally mindful	Pts pain has improved Pt feels happier, calmer, has more energy. Pt feels that she is more in the moment, with less negative thinking
No. 3 Att: 8/8 54F White Scottish DD 9 University EDSS 5.5 PPMS 0 (0) **64**	**	Pt found 'thoughts are not facts' allowed her to let go of thoughts and worries which has meant she is now sleeping better instead of lying awake fretting	Pt more aware of her father's suffering and has a feeling of compassion towards him. Has used Mindful skills to relate to him when he is struggling. Friends have commented how happy pt is, which she puts down to learning Mindfulness	Pt feels much more in control of what is happening in her life, feels less stressed. Pt is walking better and feeling stronger. Pt feels more content, is calmer and is sleeping better (less wakening, more refreshed) and less rumination

No. 4 36M Att: 7/8 White Scottish DD 3 2y school EDSS 2.5 RRMS 9 (3) **58**	**	Pt describes being more aware of the need to practise regularly	Pt had his social anxiety challenged by coming to the group, but managed to come to almost all sessions	
No. 5 Att: 7/8 65F White Scottish DD8 2y school EDSS 5 RRMS 9 (2) 75	Pt found it useful to both do the practice, and then to discuss it Pt liked being led through the practice Pt really liked the poetry	Pt is being kinder to herself, less critical and judgemental of herself Pt describes being more likely to think before speaking	Pts spouse commented to her that she seemed happier and was being nicer to him	Numbness in pts feet and hands is improved Pt is walking more slowly and mindfully and thinks this makes falling less likely Pt is feeling calmer, is feeling more and noticing more
No. 6 Att: 7/8 44 F White Scottish DD 8 University EDSS 6.5 RRMS 5 (2) **49**	Pt thought meditation on arrival helped calm the group Pt found the poetry touching	Pt realised she wasn't doing enough to rejuvenate herself, and that it was all chores Pt recognized she found it easier to offer compassion to another than to herself Pt feels more in control and is taking the day in chunks		Pt feels she has less mind chatter, less anxiety Pt more aware of her thoughts and behavior and their impact Pt feels she is more in the moment
No. 7 Att: 3/8 52F	Pt liked the Mountain meditation, being able to sink in and connect with the earth,		Pt has used Mindfulness skills to deal with family relationship difficulties	Pt feels more relaxed and chilled, less worried and anxious

White Scottish DD 2 College EDSS 6.5 RRMS 5 (1) **63**	linked the seasons metaphor to the seasons of her life			
No. 8 Att: 7/8 34F White Scottish DD 3 University EDSS 3.5 RRMS 5 (1) **72**	Pt described seeing something that had previously terrified her in a new light (a bird), which made her feel amazing Pt loved being guided through the practice on the floor Pt describes that on hearing the bells, you immediately went into the zone Pt found that the longer practices were easier to get into the zone, and that she adapted the shorter practices to make this easier, such as using a painting or apple instead	Pt describes no longer taking herself for granted anymore, is more confident being herself, and is no longer giving of herself when she has nothing left to give	Pt realized that she had to share her struggles with her family, to let them in, to stop having a wall around herself, and to get real confidence, as opposed to that which is fake	Left foot pain is better Pt feels happier, calmer and more confident, grateful, less stressed and more relaxed, more together emotionally, with a stronger core. Pt less prone to avoiding difficult emotions Pt feels less muddled up
No. 9 Att: 2/8 48F White Scottish DD 5 2y school EDSS 7 RRMS 1 (0) 84	Pt found sitting in the class difficult, as she could not relax, and describes herself as someone who doesn't relax			Pt thought that the focus of the course participants was too negative and that she has found staying positive more helpful. Pt felt she needed more out of the course.
No. 10 Att: 7/8 43F		Pt decided during the course that she could only do what she could and she		Pt feels calmer, especially in a crisis

White Scottish DD 7 University EDSS 7 RRMS 1 (0) **71**		was no longer going to beat herself up about this		
No. 11 Att: 8/8 27F White Scottish DD 6 University EDSS 6 RRMS 4 (1) **66**		Pt described recognizing that she was not being very nice to herself and that this needed to change Describes being more aware of things getting out of hand and recognising the need to practise to offset this	Pt realized that she was moving too fast in life and that she needed to slow down and appreciate her time with her daughter **	Pt thinks that she is walking better, more on the flats of her feet Pt feels calmer and that she is living more in the moment
No. 12 Att: 5/8 38F White Scottish DD 3 College EDSS 2.5 RRMS 5 (2) 79				Pt thinks her balance has improved Pt feels less stressed and more committed
No. 13 Att: 1/8 46F White Scottish DD 3 University EDSS 4 RRMS				Pt found the chronic pain and paraesthesias that she has in her hands was made worse by bringing Mindful awareness to them on the day she attended. Feels that her mental health took a dunt and that she is still a bit raw on this front

8 (0) 100				
No. 14 32F Att: 8/8 White Scottish DD 10 College EDSS 4 RRMS 6 (2) **42**	Pt found it easier to concentrate in the group, and was initially struggling at home, but then found something clicked for her and the practices became a pleasure to do. Pt thinks that BS helped her to tune into the body in a non-judging, non-critical way	Pt realised a propensity towards beating herself up a lot and not to appreciate what she does well Pt is taking more interest in health promoting behaviours such as exercise and diet	Pt describes a situation at a party, where a man pushed a balloon into her face - in the past she would have reacted, possibly with a confrontation. Pt was far more reflective in the situation, and gained insight into his motivations and suffering, which it turned out were due to his mother and sister having MS. Pt spoke to him and counseled him about this. Pt using Mindful skills to help another family member with anxiety.	Pt is feeling more back to her old self and is happier Pt has noted a positive change in her attitude towards her chronic pain Pt feels less highly strung and more positive Pt thinks she is less short of breath from anxiety
No. 15 Att: 1/8 40F White Scottish DD 4 College EDSS 1 RRMS 2 (0) 103				Pt felt unwell from attending on week 1, thinks this was from seeing and being around so many negative, moaning people. Pt felt this posed a risk to her health, so did not come back. Saw herself ending up in a wheelchair with a chronic condition. Pt felt that the focus of the course should have been more firmly on ability Pt felt that the other participants were being negative, that it was a greeting meetin, and that they needed counseling, not meditation. Pt thought the negativity affected her. Pt thinks a positive attitude is more helpful.
No. 16 Att: 7/8 44M White Scottish DD 8	Pt found being shown how to do the practices really helped		Pts partner saw a difference in him when practicing. Pt was getting less annoyed with work colleagues and experiencing less road rage.	Pt feeling less uptight and stressed, calmer, and more chilled, better able to let go of things, and that the critical voices in his head have become less prominent

University EDSS 6.5 RRMS 0 (0) **53**				
No. 17 Att: 6/8 36F White Scottish DD 3 University EDSS 2.5 RRMS 2 (1) 75	Pt found the meditation exercises were easier in a group, with everyone doing the same thing, facilitating concentration	Pt describes having insight into why she doesn't practise, in that she prioritizes other things		Pt felt calmer on leaving the classes
Course instructors				
I1		Ins found this a challenging course. Talked with other ins and colleagues at the Centre about this, and took the difficult aspects of the experience to supervision		
I2				

4. Improving the MBSR course for people with MS	**4.1**	**4.2**	**4.3**	**4.4**
Subject no **No. sessions attended** **Age** **Sex** **Ethnicity** **Deprivation decile Education** **EDSS** **MS phenotype** **MM count (MH)** **MHI baseline score**	**Making MBSR more relevant to people with MS**	**Being better prepared**	**Improving delivery strategies of MBSR for people with MS**	**Timing: when is the best time to learn MBSR if you have MS?**
No. 1 Att: 7/8 52F White Scottish DD 2 University EDSS 4 PPMS 3 (1) **69**	Pt planning to use her Mindfulness skills in dealing with the stress of returning to work, when communicating with others, and when managing uncertainty. Varies the practice, depending on what she is faced with	Pt would like for there to be more time to socialize with other pts		
No. 2 Att: 6/8 41F White Scottish DD 2 University	Pt now sees Mindfulness as her hobby and wants to learn more about it and is thinking of taking up Yoga. Practices MM 2x/wk Pt tries to be mindful whilst doing things through the day			Pt did not like mans voice on the CDs

EDSS 4 RRMS 3 (1) **46**	Planning to attend drop in sessions			
No. 3 Att: 8/8 54F White Scottish DD 9 University EDSS 5.5 PPMS 0 (0) **64**	Practises daily and feels confident about this Uses 3MBS as a security blanket Pt has found practices useful in acute stress situations Pt has found dissociating helpful in stressful scenarios	Pt thinks an introductory day would help, where expectations could be addressed, pt testimonials shared, let people know in advance about needing a CD player, letting family know what is involved	Pt would like to see more on the research science associated with MBSR	Pt thinks it needs to be made clearer how important HP is
No. 4 36M Att: 7/8 White Scottish DD 3 2y school EDSS 2.5 RRMS 9 (3) **58**	**	**		Pt thinks there should be less led exercises so that people can learn to do it on their own Pt thinks that for some of the meditation exercises people could have been better prepared physiologically
No. 5 Att: 7/8 65F White Scottish DD8 2y school EDSS 5 RRMS 9 (2) 75	**			Did not like FCL, but did like MBCT book

No. 6 Att: 7/8 44 F White Scottish DD 8 University EDSS 6.5 RRMS 5 (2) **49**	Pt would like to attend drop in sessions, but as they are in the seminar room this is a barrier for her	Pt thinks course should be informed by someone with MS who has been unwell Pt thinks course should not be held over lunchtime	Pt thinks it should be more MS specific Pt thinks MW should only be included if ability appropriate Pt thinks there should be more group interaction and that instructors should remember that impaired mobility can impair mingling	Pt thinks Ins should be more sensitive to the needs of people with MS Pt thinks the CDs could be shorter
No. 7 Att: 3/8 52F White Scottish DD 2 College EDSS 6.5 RRMS 5 (1) **63**	Pt uses breath awareness as a means of managing sleep difficulty and a s a way of relaxing	Pt thinks Tea/ coffee should be in the room	Pt thinks manual should cover a wider range of ability levels	Pt thinks the course should be shortened to 4-6/52. Pt thinks more emphasis should be placed on HP Pt thought not too soon after the Dx, as the whole thing might be a bit raw
No. 8 Att: 7/8 34F White Scottish DD 3 University EDSS 3.5 RRMS 5 (1) **72**	Pt has been looking to carry on the practices and uses Youtube to find new ones too	Should be closer to pts home Should be more disability friendly from the start		Ins should be firmer about importance of HP Pt did not like mans voice on the CD, found it 'shouty'
No. 9 Att: 2/8 48F White Scottish		**	Should include more physical exercise	

DD 5 2y school EDSS 7 RRMS 1 (0) 84				
No. 10 Att: 7/8 43F White Scottish DD 7 University EDSS 7 RRMS 1 (0) **71**	Pt uses materials flexibly Uses shorter practices to help herself calm down and reassess things	Pt thinks course should be informed by someone with MS Extra help should be on hand	Pt thinks materials should be more MS-specific, with exercises specifically for pain etc	Pt thinks that pt input should be garnered at the time of the course itself Pt didn't like mans voice on CD; liked female voice on CD as it was soothing Pt wished she had had the opportunity to learn Mindfulness around the time of her Dx to help her cope
No. 11 Att: 8/8 27F White Scottish DD 6 University EDSS 6 RRMS 4 (1) **66**	Pt still practicing, but less of a range Notes that being immersed in the practices helped	Pt would prefer it to be held later in the day	Pt would prefer last day was more about meditation, and less about filling in forms	
No. 12 Att: 5/8 38F White Scottish DD 3 College EDSS 2.5 RRMS 5 (2)	Pt found knowing that there was a class next week helped her keep up the practices – an incentive of sorts	Pt thinks being able to contact the instructors during the course would help		

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No. 13 Att: 1/8 46F White Scottish DD 3 University EDSS 4 RRMS 8 (0) 100		Pt thinks a greater understanding over the practical difficulties associated with MS should be used to inform design etc		
No. 14 32F Att: 8/8 White Scottish DD 10 College EDSS 4 RRMS 6 (2) **42**	Pt thinks her changed way of thinking has made her less stressed in day to day life - moving house was much less stressful than anticipated Planning to attend drop in sessions			
No. 15 Att: 1/8 40F White Scottish DD 4 College EDSS 1 RRMS 2 (0) 103		Pt thinks mixed Dx would work better	Pt thinks it should be more like 'Mindstore'. Pt thinks it should have a more positive focus	Pt thinks to be careful with words like 'exercise', which can easily be misinterpreted. Pt thinks there should be personal goal setting for pts. Pt thinks pts should be encouraged to challenge themselves Pt thinks manual and materials should be more MS specific
No. 16 Att: 7/8 44M	Pt found the practices were helpful when he was practicing, and will go back to them once relapse settles.	Pt thinks testimonials from completers would help Pt thinks an orientation session would help		Pt thinks visual aids would help Pt thinks best not to start

White Scottish DD 8 University EDSS 6.5 RRMS 0 (0) **53**				with the RE
No. 17 Att: 6/8 36F White Scottish DD 3 University EDSS 2.5 RRMS 2 (1) 75				
Course instructors				
I1			Thinks MBSR well sculpted	Ins thinks need for caution around MW
I2		Ins thinks OS is needed		Ins would be cautious about language